THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JANUARY, 1953

ORIGINAL ARTICLES

CATION EXCHANGE RESIN THERAPY IN PATIENTS RECEIVING CORTISONE OR ACTH*

By LAWRENCE GREENMAN, M.D.
RENZIEHAUSEN ASSISTANT PROFESSOR OF RESEARCH MEDICINE

F. A. WEIGAND, M.D.
RENZIEHAUSEN FELLOW OF RESEARCH MEDICINE

AND

T. S. DANOWSKI, M.D.
RENZIEHAUSEN PROFESSOR OF RESEARCH MEDICINE

(From the Department of Research Medicine, University of Pittsburgh School of Medicine, and the Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania)

IT has been suggested that certain of the changes in body electrolytes induced by synthetic cation exchange resins might prove useful in counteracting or deferring the toxic effects of prolonged or massive cortisone or ACTH therapy[1,8]. Thus, disregarding for the moment their modes of origin, the hyperchloremia and metabolic acidosis which follow ingestion of an acidifying resin[2,7] could offset the hypochloremia and alkalosis produced by cortisone and ACTH. Similarly, the increased fecal excretion of sodium noted in subjects receiving these exchangers might minimize the sodium retention and edema which develop in patients receiving these hormones. This latter effect would also permit a more liberal intake of sodium. Finally, precharging some of the exchanger with potassium would augment the intake of this ion and perhaps thereby prevent the potassium depletion which develops during steroid or ACTH therapy. The feasibility and practicality of this approach has been tested in a series of studies.

Materials and Methods. Five children receiving either cortisone or ACTH, or both, in treatment of active rheumatic fever each day ingested 80 gm. of a synthetic cation exchange resin of the carboxylic type, equally divided between the hydrogen and the potassium forms for a total of 48 to 63 days. During this time the patients were maintained on a variety of dietary regimens ranging from a milk formula of exact composition to essentially unrestricted diets in which sodium content was known in terms of general orders of magnitude.

Prior to treatment and usually at weekly intervals thereafter, samples of fasting blood

* This study made possible by a grant-in-aid from the United States Public Health Service and the Western Pennsylvania Chapter of the Arthritis and Rheumatism Foundation.

TABLE 1.—BODY WEIGHT AND ANALYSES OF BLOOD AND SERUM DURING CORTISONE OR ACTH AND EXCHANGE RESIN THERAPY OF ACUTE RHEUMATIC FEVER

Subject (Age-Sex)	Time† (days)	Therapy: Cort. (mg./d)	Therapy: ACTH (mg./d)	Therapy: Resin H^+ (gm./d)	Therapy: Resin K^+ (gm./d)	Body Wgt. (kg.)	Blood: Sugar (mg./100 cc.)	Blood: NPN (mg./100 cc.)	Serum: HCO_3 (mEq./L.)	Serum: Cl (mEq./L.)	Serum: Na (mEq./L.)	Serum: K (mEq./L.)	Serum: Chol. (mg./100 cc.)	Serum: P (mg./100 cc.)	Serum: Prot. (gm./100 cc.)	Blood Eos. /c.mm.
D. P.	0	0	0	0	0	36.7	84	42	—	92.8	136	4.3	188	—	7.8	6
12 M	0-2	300	0	40	40	—	83	40	25.8	100.7	—	—	271	5.4	7.0	6
	2-7	300	0	40	40	35.9	—	47	20.4	103.9	146	4.2	257	4.9	6.6	0
	7-14	300	0	40	40	35.0	88	42	22.5	102.3	140	3 8	329	3.5	5.9	6
	14-21	300	0	40	40	39.1	73	29	32.2	92 8	148	3.0	279	3.3	5 9	19
	21-28	300	0	40	40	36.9	65	38	27.0	100.2	143	3.4	350	3.4	6.4	25
	28-35	300	0	40	40	36.3	84	38	24.5	98.4	—	4.0	360	4.1	6.1	6
	35-42	300	0	40	40	37.0	85	42	22.0	99.3	138	3.6	394	4.3	—	19
	42-49	0	0	40	40	36.8	—	38	—	—	—	—	—	5 2	6.5	—
	49-56	0	0	40	40	36.8	83	40	25.8	100.7	147	4.3	271	5.4	7.0	0
H. B.	0	0	0	0	0	39 5	87	39	23.9	102.0	146	4.4	296	5 0	8 3	113
10 F	0-7	300	0	40	40	41.3	78	28	26.3	100.1	143	3 8	178	4.7	7.9	38
	7-14	300	0	40	40	41.8	92	34	30.0	—	143	3.7	219	4.5	7.3	0
	14-21	300	0	40	40	41.5	73	38	26.4	99.9	143	3.6	255	4.8	6.4	0
	21-28	300	0	40	40	42.0	69	34	—	95.4	143	4 0	230	4.5	5.3	0
	28-35	300	0	40	40	43.2	87	36	28.3	101.7	146	4.4	159	4.3	7 0	0
	35-42	300	0	40	40	44.0	79	36	28.3	96 5	143	4.4	—	—	7.6	31
	42-49	243	0	40	40	44 5	—	—	—	—	—	—	—	—	—	38
	49-56	79	0	40	40	45.2	—	38	—	—	—	—	—	—	6.2	81
	56-63	0	0	0	0	45.8	—	34	—	—	—	—	—	—	7 3	—
J. L.	0	0	0	0	0	36.7	66	29	25.4	90.4	140	4.4	179	5.2	7 8	19
12 M	0-7	0	100	40	40	34.3	89	47	21.9	96.9	134	4.8	171	5.5	8.3	19
	7-14	0	100*	40	40	35.6	83	36	—	92.7	138	4,0	251	4.8	7.5	56
	14-21	200	0	40	40	36 2	81	34	28.2	92.2	143	4.3	267	4.6	7.2	6
	21-28	200	0	40	40	37 1	89	36	25.3	91.4	—	4.1	296	4.3	7.4	0
	28-35	200	0	40	40	37 2	70	34	28.7	95.6	142	3.9	254	4.6	7 0	—
	35-42	200	0	40	40	38.8	71	34	26.3	93.6	142	3 9	312	3.5	7 0	13
	42-49	143	0	40	40	39 0	97	27	25.8	96.0	144	3.4	—	—	6.7	25
	49-54‡	20	0	40	40	39.4	96	31	22.8	99.7	142	4.2	—	—	7 4	50
	54-63	0	0	40	40	38.5	—	29	—	—	—	—	—	—	5 8	37
L. S.	0	0	0	0	0	—	64	34	25.3	95.8	141	4.5	—	5.0	7.2	400
13 M	0-7	0	100	40	40	31.3	82	44	21.0	95.5	140	4.2	457	4.8	7.4	0
	7-14	0	100	40	40	30.9	94	38	24.9	93.7	136	3.6	312	4.5	7.2	0
	14-21	0	100	40	40	35.4	99	34	32.8	89.4	142	2.0	318	3.4	5.9	0
	21-27	0	100	40	40	36.7	100	43	22.9	87.6	—	2.6	306	3.4	5.9	0
	27-34	0	100	40	40	36.8	95	35	28.6	93.6	142	2.8	318	3.3	4.6	0
	34-41	0	100	40	40	37.9	102	38	30.1	95.6	144	2.5	350	3.8	5.9	0
	41-48	0	83	40	40	37.7	113	27	32.7	97.1	144	2.8	—	3.4	5.8	0
	48-52	0	30**	0	0	38.6	91	38	28.2	98.5	147	4.3	—	—	5.4	—
R. R.	0	0	0	0	0	26.4	105	39	23.4	95.8	141	4.7	282	4.8	7.7	13
10 M	0-7	0	100	40	40	26.6	121	45	28.3	95.8	146	5.9	—	—	6.7	0
	7-14	0	100	40	40	29.3	—	—	—	—	—	—	—	—	—	0
	14-21	0	89	40	40	28.8	—	39	29.7	95.6	142	4.3	—	—	6.4	0
	21-28	0	60	40	40	—	—	42	26.6	100.7	139	3.0	—	—	5.5	6
	28-35	0	60	40	40	31.9	—	50	28.5	98.3	138	3.8	—	—	6.0	6
	35-42	0	58	40	40	33.6	—	41	28.8	98.6	142	4.3	—	—	6.4	—
	42-49	0	39	40	40	33.5	—	46	27.0	95.4	142	4.3	—	—	6.9	—
	49-56	0	30	40	40	—	—	40	24.4	106.7	—	—	—	—	6.4	—
	56-63	0	0	0	0	—	—	32	24.5	99.2	140	5.3	—	—	6.4	—

were withdrawn for eosinophil counts[9], blood NPN and sugar determinations, and serum bicarbonate, chloride, sodium, potassium, phosphorous and cholesterol measurements[3]. Body weights were obtained at the same time.

Complete collections of stools available from 17 of the 44 study periods have been analyzed for chloride, sodium, potassium, and nitrogen[7]. In 3 of the periods with a known intake, complete urine collections were made and external and internal balances of constituents under study have been calculated[2].

treatment with similar or larger amounts of cortisone or ACTH has been listed in Table 2. There is no evidence that the ingestion of the two exchangers lessened the incidence or the degree of hypochloremia, or of serum CO_2 elevation. Hypokaliemia was, however, more frequent in the resin treated group since 4 of the 5 patients developed potassium concen-

TABLE 2.—INCIDENCE OF HYPOKALIEMIA, ALKALOSIS AND HYPOCHLOREMIA DURING THERAPY OF ACUTE RHEUMATIC FEVER IN A CONTROL GROUP OF PATIENTS TREATED WITH ACTH OR CORTISONE ALONE COMPARED TO THE INCIDENCE IN THE PRESENT SERIES IN WHICH RESINS WERE ADDED

Therapy	*Total Number of Patients Treated*	*Number with Serum $K^+ < 3.5$ mEq./L.*	*Number with Serum $HCO_3 > 28.0$ mEq./L.*	*Number with Serum $Cl < 96.0$ mEq./L.*
Cortisone	63	6	26	37
ACTH	12	1	5	5
Cortisone + Resins	3	2	3	3
ACTH + Resins	2	2	2	2

Results. A. SERUM AND BLOOD ANALYSES. The concentrations of serum and blood constituents in this group of patients are presented in Table 1. It is immediately evident that these ill children tended to have low serum chlorides prior to therapy while the serum CO_2 content, and the serum potassium and sodium concentrations were usually unaltered. During treatment transient or persistent decreases in serum potassium were observed together with intermittently high serum CO_2 levels and fluctuating concentrations of chloride. The sodium values remained relatively constant. To provide a basis for interpretation the incidence of abnormal serum concentrations of potassium, bicarbonate, and chloride in 75 other children with acute rheumatic fever undergoing

trations of 3.4 mEq./L., or less, without clinical symptoms.

It is our impression that hypokaliemia may have appeared more rapidly when the patients were ingesting diets unrestricted in sodium content than when sodium intake was limited to 10 mEq. per day. Thus in D.P. and L.S. abnormally low serum potassium values appeared 21 days after the start of hormone and resin therapy and 7 and 14 days, respectively, following transfer to a general diet without sodium limitation. R.R. and J.L., on the other hand, maintained on diets containing about 10 mEq. of sodium per day, did not develop hypokaliemia until the 28th and 49th days of therapy, respectively. The potassium level rose to normal in one week in R.R. despite continued resin and ACTH therapy

when supplementary $KHCO_3$, 8 gm. per day was administered in divided doses. In L.S., however, the hypokaliemia did not disappear until the resin was discontinued after the 48th day even though extra potassium had been given in the form of meat extract.

Only brief comments need be made concerning the other components of Table 1. The blood sugar fluctuated within the usual fasting range without any instance of hyperglycemia. The levels of NPN tended to be borderline or slightly elevated, presumably as a manifestation of the rheumatic state with impaired cardiorenal function and increased protein catabolism. Patients D.P. and J.L. developed a progressive hypercholesterolemia. The initially high total serum proteins attributable in part at least to dehydration present on admission, and hyperglobulinemia returned to normal levels during therapy. The eosinophil counts were usually low or zero. These findings are quite comparable to those observed in a larger group of rheumatic children who were treated with cortisone or ACTH but did not receive cation exchange resins.

B. Stool Data. Since the daily allotment of resin contained 150 mEq. of potassium while stool output of this cation only once exceeded this amount (Table 3), it can be stated with assurance that some of the potassium present on the resin was released and absorbed. The remainder was excreted in the feces, since the stool content of this ion was always considerably greater than that seen when a non-potassium exchanger was administered. Complete balance data are not available during the periods in which hypokaliemia appeared.

Insofar as fecal sodium is concerned there is no question but that the exchange resin usually increased the output of this ion considerably above control levels. These increments were without exception much smaller than the concomitant increases in the excretion of potassium. As in previously published studies, occasional unexplained low sodium values were observed (Patient D.P.). They were not related to the administration of either cortisone or ACTH since the stool excretion of electrolytes was quite comparable with both of these agents. During ACTH therapy there was no significant change in the amount of sodium excreted in the stool from that present when cortisone was administered, (periods 0 to 7 and 7 to 14 with ACTH in J.L. compared with subsequent intervals on cortisone in the same patient) (Table 3). On the other hand the stool excretion data do indicate that in some instances endogenous sodium was removed by the exchanger. This is readily evident from comparisons of the intake and stool output data in patient D.P., periods 28 to 35 and 42 to 49; patient J.L., all periods from 0 to 42 days; and intervals encompassed between days 34 and 41 in L.S. On a general diet the stool output of sodium in this last patient was in the same range of magnitude as that recorded on a diet which contained 35 mEq. of sodium per day.

As in previously published studies[2, 5,7,8] the stool chloride and nitrogen excretion in all of these patients were not discernibly affected by resin therapy.

C. Water, Electrolyte and Nitrogen Exchanges. It is to be noted that all patients in this series gained weight during one or another portion of these studies. It is probable that except in patients D.P. and L.S. this reflected in the main an improved nutritional status mediated directly or indirectly through the hormone therapy and concomitant clinical recovery. In D.P. and L.S.,

TABLE 3.—INTAKE DATA AND URINE AND STOOL OUTPUT DURING CORTISONE OR ACTH AND EXCHANGE RESIN THERAPY OF ACUTE RHEUMATIC FEVER

Subject	Therapy					Intake					Urine					Stool				
	Time (days)	Cort. (mg./d)	ACTH (mg./d)	Resin H^+ (gm./d)	Resin K^+ (gm./d)	Fluid (l.)	Cl (mEq.)	Na (mEq.)	K* (mEq.)	N (gm.)	Vol. (l.)	Cl (mEq.)	Na (mEq.)	K (mEq.)	TN (gm.)	Wgt. (gm.)	Cl (mEq.	Na (mEq.)	K (mEq.)	N (gm.)
D. P. 12 M	0–7	300	0	40	40	17.4	371	306	1486	96.6	8.5	36	19	241	102.6	1042	4	4	628	4.8
	7–14	300	0	40	40	14.9	386	319	1504	100.6	8.3	48	39	222	105.8	1664	9	303	1108	6.8
	14–21	300	0	40	40	General diet														
	21–28	300	0	40	40	10 mEq./d. sodium diet														
	28–35	300	0	40	40	"	"	"								1677	—	256	894	11.5
	35–42	300	0	40	40	"	"	"								1213	—	10	683	7.0
	42–49	0	0	40	40	"	"	"								2333	—	104	243	8.2
	49–56	0	0	0	0	"	"	"												
J. L. 12 M	0–7	0	100	40	40	10 mEq./d. sodium diet										1391	2	319	632	6.0
	7–14	0	100	40	40	"	"	"								2091	—	176	996	10.1
	14–21	200	0	40	40	"	"	"								1982	1	138	770	11.2
	21–28	200	0	40	40	"	"	"								1236	—	126	503	7.4
	28–35	200	0	40	40	"	"	"								1766	—	205	612	9.1
	35–42	200	0	40	40	"	"	"								2590	—	231	828	15.0
L. S. 13 M	0–7	0	100	40	40	—	444	367	1572	108.7	5.4	218	59	294	53.8	1080	—	297	536	5.2
	7–14	0	100	40	40	General diet										1462	—	138	745	5.5
	14–21	0	100	40	40	General diet without salt										3520†	25	168	860	17.0
	21–27	0	100	40	40	35 mEq /d. sodium diet										1647†	12	143	370	11.7
	27–34	0	100	40	40	"	"	"								4221†	—	228	724	27.2
	34–41	0	100	40	40	"	"	"								5698†	—	405	1061	41.6

* Includes K supplied by resin (3.75 mEq./gm. of resin)

TABLE 4.—EXTERNAL, EXTRACELLULAR, AND CELL BALANCES DURING CORTISONE OR ACTH AND EXCHANGE RESIN THERAPY OF ACTIVE RHEUMATIC FEVER

		Therapy				External Balance				Extracell. Bal.			Cell. Bal.		
	Time	Cort.	ACTH	Resin H^+	Resin K^+	Cl	Na	K	N	H_2O	Na	K	N'	Na	K'
Subject	(days)	(mg./d)	(mg./d)	(gm./d)		(mEq.)	(mEq.)	(mEq.)	(gm.)	(l.)	(mEq.)	(mEq.)	(gm.)	(mEq.)	(mEq.)
D. P.	0–7	300	0	40	40	+326	+277	+627	−11.3	−0.4	+5	−2	−12.5	+272	+599
12 M	7–14	300	0	40	40	+326	−27	+174	−12.2	+0.4	+13	−2	−11.0	−40	+202
L. S. 13 M	0–7	100	0	40	40	+223	+7	+742	+54.6	+0.2	+23	−1	+52.6	−16	+618

however, most of the weight gain represented edema fluid. It is pertinent to note that this occurred when these 2 children were on a general diet unrestricted in sodium together with large amounts of exchange resin. Reduction of the sodium intake with continued resin therapy resulted in a diuresis and weight loss of 2.2 kg. in D.P. (period 21 to 28) and prevented further edema formation in L.S.

External and internal balance data are available in both of these patients *prior* to the weight gains discussed above (Table 4). In each instance the patients were in positive potassium balance but the serum potassium values nonetheless declined. The absence of edema and the presence of virtual equilibrium insofar as external balances of sodium were concerned, excludes the possibility that these decreases in serum potassium were attributable to dilution of the extracellular fluid. Inevitably potassium must have been transferred to the extrachloride spaces. The magnitude of these transfers is recorded in the K^1 column of the cell balance section of Table 4. It is of interest that in patient D.P. the cell potassium balance was positive even though the patient was losing nitrogen.

Discussion. From the data which have been presented it is clear that this mixture of exchange resins did exert its established effects on stool composition, but did not control the manifestations of ACTH and cortisone toxicity. Despite the increased output of sodium in stools, control of edema could be achieved only by the concomitant use of sodium restricted diets. This increase in stool sodium was accomplished without losses of body potassium through the gastrointestinal tract. As a matter of fact an increment was added to the dietary intake as a result of assimilation of potassium displaced or released from the resin. This additional supply of potassium was not sufficient to prevent a high incidence of hypokaliemia in these patients. The frequency of low potassium values may actually have been increased despite the absorption of some potassium from the resin. It seems reasonable to suggest that the potassium was lost from the body via the kidneys since these hormones alone may produce deficits of body potassium and hypokaliemia as a result of increased urinary losses of the ion. The possibility that the potassium was stored in the cells at the expense of the extracellular content of the cation does not seem likely. The small number of patients in the study, however, limits the generalizations which may be made from these data. The validity of our observations are strengthened by Bonner's similar findings in 4 adults treated with ACTH and sulfonic resins[1], and by our previous experience with therapy combining acidifying carboxylic exchangers and ACTH or cortisone[8]. In both of these studies the resin combination contained only 20% in the potassium form. The administration of the potassium form of the exchanger alone would probably prevent hypokaliemia but would not permit significant liberalization of sodium intake.

Although the incidence of alkalosis and of hypochloremia during therapy with cortisone or ACTH was not reduced by the addition of the acidifying exchangers, the acidosis and the hyperchloremia which usually follow ingestion of these amounts of H+ form resin were not observed. This may have been the result of the concomitant hormone treatment or the large portion of non-acidifying resin in the mixture.

Despite the small number of patients in the present study, it seems reasonable to conclude that these particular resins do not offer as satisfactory a

method of controlling the acid-base and mineral effects of cortisone and ACTH therapy as do adequate sodium restriction plus supplementary KCl.

Summary and Conclusions. 1. The concomitant use of exchange resins (carboxylic type with equal parts of hydrogen and potassium forms) did not prevent alkalosis or hypochloremia of ACTH or cortisone therapy.

2. Release of potassium from ingested resin provided some increase in the amount of assimilated potassium but did not prevent the development of hypokaliemia in 4 of the 5 patients.

3. The resins increased the stool output of sodium. This was of insufficient magnitude to prevent edema formation of cortisone or ACTH origin in patients on an unrestricted diet.

REFERENCES

1. **Bonner, C. D.:** New Eng. J. Med., **247,** 158, 1952.
2. **Danowski, T. S., Greenman, L., Mateer, F. M., Parsons, W. B., Weigand, F. A., Mermelstein, H.,** and **Peters, J. H.:** J. Clin. Invest., **30,** 984, 1951.
3. **Danowski, T. S., Peters, J. H., Rathbun, J. C., Quashnock, J. M.,** and **Greenman, L.:** J. Clin. Invest., **28,** 1, 1949.
4. **Greenman, L.,** and **Danowski, T. S.:** Unpublished data.
5. **Greenman, L., Danowski, T. S., Tarail, R., Peters, J. H., Weigand, F. A.,** and **Mateer, F. M.:** J. Clin. Invest., **30,** 644, 1951.
6. **Greenman, L., Peters, J. H., Mateer, F. M.,** and **Danowski, T. S.:** J. Clin. Invest., **30,** 1027, 1951.
7. **Greenman, L., Peters, J. H., Mateer, F. M., Weigand, F. A., Wilkins, D., Tarail, R., Rhodes, G.,** and **Danowski, T. S.:** J. Clin. Invest., **30,** 995, 1951.
8. **Peters, J. H., Danowski, T. S., Greenman, L., Weigand, F. A., Clarke, C. E., Garver, K., Mateer, F. M.,** and **Tarail, R.:** J. Clin. Invest., **30,** 1009, 1951.
9. **Roche, M., Thorn, G. W.,** and **Hills, A. G.:** New Eng. J. Med., **242,** 307, 1950.

ANTICOAGULANT THERAPY IN ACUTE MYOCARDIAL INFARCTION.

A SURVEY OF SPECIALISTS' OPINIONS CONCERNING INDICATIONS, RESULTS AND DANGERS.

By Henry I. Russek, M.D.
CONSULTANT CARDIOLOGIST, U.S.P.H.S. HOSPITAL
STATEN ISLAND, NEW YORK

AND

Burton L. Zohman, M.D.
CLINICAL ASSOCIATE PROFESSOR, STATE UNIVERSITY COLLEGE OF MEDICINE
AT BROOKLYN, NEW YORK

Accumulating reports in world medical literature appear to indicate that anticoagulant therapy merits an important place in the management of acute myocardial infarction. In spite of the overwhelming evidence in favor of this mode of therapy, however, it is by no means certain that all patients afflicted with this disease should be routinely treated in this manner. Many physicians in general practice as well as specialists in internal medicine or cardiovascular disease do feel obliged to use an anticoagulant drug in every patient who sustains an attack of acute myocardial infarction. In some instances this attitude is doubtless based on a firm personal conviction regarding the value of this form of treatment. In others, it takes origin from the pronouncement[9] that anticoagulants should be employed in all cases of this disease "since it is impossible to predict from the condition of the patient during the first week whether thromboembolic complications will develop during subsequent weeks and whether death will occur from them." Many physicians who remain unconvinced or uncertain regarding the benefits to be derived from anticoagulant drugs continue their routine use chiefly because of fear of criticism by colleagues or of reproach by patients or their families who have been enlightened by medical articles in the lay press. Some doctors have candidly expressed real apprehension at the thought of possible litigation for malpractice if death or complications were to develop in some of their patients not receiving these drugs.

Regardless of one's personal reasons for prescribing anticoagulant therapy, its administration requires hospitalization for many patients who could otherwise be treated satisfactorily at home. It increases the cost of medical care by the necessity for hospitalization, the added expense of laboratory tests and the greater number of visits required of the attending physician. It is contributing to the overcrowding in our hospitals and to the burden placed on the laboratory facilities of these institutions. There is good reason to believe that it may well be worth its price in the more serious cases of acute myocardial infarction, but whether or not this can also be claimed for the milder cases of the disease has become a subject of editorial comment[2,3], investigation[1,6,7] and debate[4,8].

In previous studies[6,7] the authors observed that there is a strikingly low mortality rate and incidence of thromboembolism in selected "good risk" cases treated by conservative methods, exclusive of anticoagulant drugs. Among such patients (those showing no serious prognostic signs within the first 24

hours of admission to the hospital) the theoretically preventable mortality and morbidity under dicumarol appeared too meager to justify the hazards entailed in its use. From the data obtained, moreover, one could not even dismiss the possibility that in "good risk" cases, greater obstacles to uneventful recovery might be encountered under dicumarol than under conservative treatment.

In order to determine the present views regarding anticoagulant therapy for acute myocardial infarction, an analysis was undertaken of the current practices of leading internists and cardiologists in various medical centers throughout the United States. Through the medium of a questionnaire which was forwarded to several hundred physicians selected from the Directory of Medical Specialists, a cross-section of authoritative opinion was sought concerning the value, limitations and dangers of this form of treatment. Included in this survey were many of the foremost names in American medicine. It was hoped that the data obtained in this manner, might assist the practising physician in formulating a tentative plan of therapy pending final solution of his present dilemma. This report is based on an analysis of the 228 replies which were received in answer to the following questions:

1) If no contraindications exist, do you employ anticoagulants in all cases of acute myocardial infarction?

2) If not, how do you select your patients for anticoagulant therapy?

3) Have you personally observed instances of serious hemorrhage or death from the use of anticoagulant drugs?

4) Which anticoagulants are you now using?

5) Do you initiate therapy with heparin?

Results of Survey. Of the 228 physicians who responded to the questionnaire, 116 or 50.9% reported that they do not prescribe anticoagulants routinely for all patients with acute myocardial infarction (Table 1). Five of the latter group of physicians actually asserted that they never use these drugs under any circumstances because they are "not convinced that the information to date warrants the assumption that the benefit from this therapy outweighs its potential hazards." The remaining 111 physicians in this group enumerated various factors in the history, physical examination and laboratory findings which assist them in deciding whether or not anticoagulants are indicated in the individual case. The only other time that they employ these agents is when forced to do so by the patient's family or the referring doctor. Eight of the 111 physicians expressed a preference for early ambulation and stated that they use dicumarol only when they feel that the patient is so sick that he will not be ambulated at an early date. The following prognostic signs were those most commonly mentioned as indicating the necessity for anticoagulant drugs: 1) previous myocardial infarction; 2) congestive heart failure; 3) the presence of a large infarct; 4) severe or persistent shock; 5) intractable pain; 6) cardiac arrhythmias; 7) significant enlargement of the heart; 8) previous thromboembolic phenomena; 9) varicosities; previous or recent thrombophlebitis or phlebothrombosis; 10) old age, debility, lethargy or marked obesity; 11) uncontrolled diabetes mellitus, polycythemia and 12) any departure from a smooth or uneventful course.

In almost every instance, hospitalization in an institution where there are facilities for adequate laboratory and clinical control was specified as a prerequisite for the administration of anticoagulant drugs. Almost all of the 111 physicians who felt that the clinical picture should be the deciding factor in the choice of treatment, expressed clear-cut indications for anti-

coagulant therapy. Six of them, however, frankly admitted that they had no precise opinion in this regard and that clinical intuition was in large measure responsible for their decision. These physicians stated that they administer anticoagulants to all of "the very sick ones but to only some of the mild ones". They are "not yet certain as to what is the right course to follow and therefore employ no specific plan of selection". A significant number of physicians reported a definite trend toward selective rather than routine use of anticoagulant drugs in the institutions with which they are affiliated. In most cases this change of attitude has been based on unimpressive statistical differences in mortality and morbidity rates between control and treated groups.

TABLE 1.—ANALYSIS OF REPLIES FROM 228 PHYSICIANS REGARDING THE ROUTINE USE OF ANTICOAGULANT THERAPY

Answer	*Comment*	*No.*	
"yes"	"with mental reservation"	10	
	"with disappointment"	6	
	without comment	64	
	with assurance	32	
		—	
			112
"no"	"never prescribe it"	5	
	"prefer ambulation"	8	
	clinical selection	97	
	clinical signs plus intuition	6	
		—	
			116
			228

The factor of age received varying emphasis with regard to its importance in relation to the use of anticoagulant drugs. Most of the physicians who reported that they administer these agents only when the clinical findings in a given case appear to favor the development of thromboembolism, supported the view that old age is in itself a special indication for such therapy. The implication is that elderly patients are more prone to thromboembolic complications because of the debility of senescense which frequently results in prolonged inactivity in bed. Opposed to this view, however, is the belief expressed by a smaller number of physicians that anticoagulants should always be withheld in elderly subjects because of the pronounced risk of serious hemorrhage. Our personal observations[5] are not wholly in agreement with either of these therapeutic dicta. Comparison of cases of similar severity in different age groups has shown that age has no influence on prognosis in the individual case. Since the clinical picture alone determines the probability of survival, the elderly "good risk" patient would not appear to be in any greater need of anticoagulant therapy than the younger "good risk" patient. On the other hand, the increased hazard of hemorrhage in older groups need not necessarily preclude the cautious use of this treatment in elderly "poor risk" patients since the evidence suggests that in the latter the benefit obtained outweighs the risk.

From the replies it is evident that the decision to employ or withhold anticoagulant drugs is often determined by certain non-medical factors among which the two most commonly mentioned were: 1) the economic status of the patient and 2) the influence of public opinion. The financial burden imposed by efficient administration of these drugs often places this form of therapy beyond the reach of many patients afflicted with this disease. The strain on family resources engendered by anticoagulant therapy coupled with the loss of income as a result of the illness itself, are regarded by some as a psychological deterrent to recovery which should not be overlooked. A number of physicians revealed that, when anticoagulants appear unnecessary, they

frequently do not feel free to exercise their judgment because of opposing pressure from the patient's family or referring doctor. The wide notoriety given to this form of therapy has created the impression that failure to employ it constitutes a culpable act of omission. Some physicians actually expressed apprehension concerning possible litigation for malpractice if death were to occur in patients not receiving these drugs.

There were 112 or 49.1% of the 228 physicians in this survey who reported that they routinely employ anticoagulants in all cases of acute myocardial infarction when no contraindications exist. Ten of this number stated that they follow this practice "because of the majority experience in the American Heart Association study." Moreover, although it is the modern teaching to employ anticoagulants in this manner, these doctors are "not at all satisfied with the conclusions drawn from the experimental work supporting this concept". Some of them have observed that failure to use these drugs "is often construed by the family, attending physician and consultant as mistreatment." Six reports expressed disappointment arising from personal experience in which thromboembolism occurred despite adequate prolongation of prothrombin time. Ninety-six physicians replied either without comment or with strong positive utterance that they employ anticoagulant drugs routinely in all cases of acute myocardial infarction. Several of this number made a point of stating that they know of no method of selection that is reliable (Table 1).

ANTICOAGULANT DRUGS. An analysis of the drugs employed by the 228 physicians responding to this survey showed that 52 prescribe dicumarol alone, 6 administer heparin alone and 9 are using Tromexan alone. Eighty-four physicians in the group prescribe dicumarol or Tromexan or Tromexan followed by dicumarol and in addition initiate therapy with heparin in the severe cases. Seventy-two physicians invariably administer heparin when prescribing dicumarol, the former being withdrawn after the first 2 or 3 days. Thus, 31.6% of the total group use heparin routinely in conjunction with dicumarol while the great majority either do not use heparin at all or reserve it exclusively for the more serious cases (Table 2).

TABLE 2.—ANTICOAGULANT DRUGS EMPLOYED BY 228 PHYSICIANS IN THE TREATMENT OF ACUTE MYOCARDIAL INFARCTION

Anticoagulant	*No. of Physicians*	
Dicumarol alone	52	
Heparin alone	6	
Tromexan alone	9	
Dicumarol with use of heparin only in severe cases	53	= 84
Dicumarol and/or Tromexan with use of heparin only in severe cases	31	
Dicumarol always with heparin at start	72	
None	5	

HEMORRHAGIC COMPLICATIONS. Of the 228 physicians whose experiences were tabulated in this survey, 104 (45.6%) reported one or more cases in which they had observed serious hemorrhage from the use of anticoagulant drugs. Approximately 70% of the same group reporting such complications advocate selective employment of this therapy based on the clinical picture in the individual case. Sixty-four physicians or 28.1% of the total group observed one or more instances in which death ensued as a direct result of hemorrhagic complications induced by anticoagulant drugs. Here again the overwhelming majority of the physicians reporting such experience (66%) belonged to the group of doctors who do not routinely prescribe this therapy. It would seem therefore

that serious untoward reactions may have played an important part in shaping the conservative attitude of many of these observers (Table 3). Serious hemorrhage was reported from almost every region of the body. Although the kidney, brain and gastrointestinal tract, in this order, were reported as the commonest sources of major hemorrhage, the brain was the chief site of fatal hemorrhage with the gastrointestinal tract and pericardium in second and third place, respectively. The observations of these physicians with respect to hemorrhagic complications were as varied as their opinions concerning the value of this form of therapy itself. Thus individual reports of the incidence of major hemorrhage varied from 0.25% with no deaths from this complication to 10% with 4 fatalities from hemorrhage among 100 dicumarolized patients.

TABLE 3.—NUMBER OF PHYSICIANS REPORTING HEMORRHAGIC COMPLICATIONS AND DEATH FROM ANTICOAGULANTS

Routine Admin.	*No.*	*Hemorr. Major*	*Death*
"yes"	112	33	22
"no"	116	71	42
Total	228	104	64

Sixty-four physicians reported a total of 122 deaths caused by anticoagulants in the treatment of acute myocardial infarction. There were 46 fatalities from brain hemorrhage: in 22 the site was subarachnoid and in 24 it was cerebral arising in the internal capsule of the brain. Thirty patients died from massive gastrointestinal hemorrhage. An old "sleeping" peptic ulcer, which was not recognized clinically or which had been quiescent for many years, was responsible for death in 20 of these cases. In the remaining 10 patients in this group, fatal hemorrhage occurred from the bowel but either no localized gastrointestinal lesion could be found at necropsy or the latter was not performed. Hemorrhagic pericarditis was reported as the cause of death in 20 patients. Although positive proof was lacking, 6 cases of rupture of the left ventricle were considered as possibly related to the use of anticoagulant drugs. Other sites of fatal hemorrhage were the kidneys, lungs, pleura and peritoneum (Table 4). Laboratory error, misinterpretation of orders by nurses and hyper sensitivity to the drug were blamed for a number of the reported deaths but the vast majority of the fatalities occurred in patients under strict control and with prothrombin and coagulation times at recommended therapeutic levels.

TABLE 4.—SITE OF HEMORRHAGE IN 122 FATAL CASES

Brain	Subarachnoid	22
	Cerebral	24
Gastrointestinal Tract	Peptic Ulcer	20
	Bowel	10
Pericardium		20
Kidneys		5
Lungs		2
Retroperitoneal		2
Unstated		17
Total		122

Summary and Conclusions. In the light of present evidence, it is by no means certain that anticoagulant drugs should be employed as a routine in all cases of acute myocardial infarction. Recent studies actually indicate that little or no benefit can be expected from their use in patients sustaining a first attack in whom no serious prognostic signs or symptoms are observed at the time of the first examination by the attending physician.

In order to determine the present opinions and current practices of leading internists and cardiologists in re-

gard to the use of anticoagulant drugs in acute myocardial infarction, a questionnaire was forwarded to several hundred specialists in various medical centers throughout the United States. On the basis of 228 replies received in this manner, the following data were obtained:

1) More than half of the 228 physicians interrogated do not employ anticoagulants as a routine measure in the treatment of acute myocardial infarction.

2) The clinical criteria determining the use of anticoagulant drugs as summarized by these physicians are: previous myocardial infarction, congestive heart failure, the presence of a large infarct, profound or persistent shock, intractable pain, significant enlargement of the heart, previous thromboembolic phenomena, varicosities, previous or recent thrombophlebitis or phlebothrombosis, cardiac arrhythmias, old age, debility, lethargy, obesity, diabetes, polycythemia and any departure from a smooth or uneventful course.

3) Most physicians in the former group regard old age as an important indication for the use of anticoagulant therapy but a significant number of them view it as a distinct contraindication. The fallacy in considering age as a significant factor in prognosis in the individual case is emphasized by the authors.

4) Among non-medical factors influencing the decision with regard to the employment of anticoagulant in this disease are: a) the economic status of the patient b) coercion by the patient's family or referring physician c) the compelling influence of the wide publicity given to this therapeutic procedure and d) the fear of criticism or even litigation for malpractice if such treatment were withheld.

5) Serious hemorrhagic complications from anticoagulant therapy were encountered by 104 or 45.6% of the 228 physicians in this survey. One hundred and twenty-two deaths caused by such complications were reported by 64 or 28.1% of the total group.

6) There was unanimity of opinion regarding the necessity for hospitalization and dependable laboratory facilities in every case in which anticoagulants are to be employed.

From these observations, it is concluded that although anticoagulant therapy now occupies an important place in the management of acute myocardial infarction, neither the evidence to date nor the current method of usage by authorities in the field can support the concept that its routine employment is necessary or desirable.

REFERENCES

1. **Baer, S., Heine, W. I.,** and **Krasnoff, S. C.:** Am. J. Med. Sci., **222**, 500, 1951.
2. Editorial: Anticoagulant Therapy of Acute Myocardial Infarction. Brit. Med. J., **2**, 991, 1950.
3. Editorial: Anticoagulant Therapy for Myocardial Infarction. Med. Ann. Dist. Columbia, **20**, 272, 1951.
4. **Foley, W. T.:** Personal communication.
5. **Russek, H. I., Zohman, B. L., Doerner, A. A., Russek, A. S.,** and **White. L. G.:** J. Am. Med. Assn., **147**, 1731, 1951.
6. **Russek, H. I., Zohman, B. L., Russek, A. S.,** and **White, L. G.:** Circulation, **5**, 707, 1952.
7. **Russek, H. I., Zohman, B. L., White, L. G.,** and **Doerner, A. A.:** J. Am. Med. Assn., **145**, 390, 1951.
8. **Wright, I. S.:** Personal communication.
9. **Wright, I. S., Marple, C. D.,** and **Beck, D. F.:** Mod. Concepts Cardiovasc. Disease, **18**, 55, 1949.

HEPARIN IN THE TREATMENT OF ADVANCED PERIPHERAL ATHEROSCLEROSIS. A Preliminary Report

By Hyman Engelberg, M.D.

AND

Theodore B. Massell, M.D.
LOS ANGELES, CALIFORNIA

The rationale for the use of heparin in atherosclerotic disease rests upon the demonstration by Graham, Gofman, *et al.*[11] that heparin has a profound effect upon plasma lipoproteins. Gofman *et al.*[10] had previously shown that the plasma lipids are carried in the form of lipoproteins of varying molecular size and density. These have been grouped into various classes characterized by their rates of flotation in the ultracentrifuge. It has been found by these workers that certain of these lipoproteins, the S_f 12-100 classes, are intimately associated with atherosclerosis in the human and in the cholesterol fed rabbit. Within a few minutes after an injection of heparin there is a progressive shift of serum lipoproteins from the larger atherogenic classes to the smaller non-atherogenic classes (Table 1). Thus the lipoprotein spectrum is altered by heparin in the direction of normality. The same workers[11] showed that heparin markedly inhibited the development of atherosclerosis in rabbits fed a high fat, high cholesterol diet. They also noted a reduction in the incidence of angina in humans treated with heparin. This finding has been confirmed in some cases by one of us[5]. While being treated for coronary atherosclerosis with heparin several patients reported decreased claudication; accordingly we began the present study.

During the past 6 months, 13 patients with severe peripheral atherosclerotic disease received intermittent doses of heparin. Although the period of observation is short, a preliminary report seems justified, in view of the definite objective and subjective improvement noted in most of the cases.

Material. All the patients selected had obliterative atherosclerosis of the lower extremities which had been present for several years in nearly all instances. One patient had xanthoma tuberosum with obstruction of the major arterial channels to one leg. Five had diabetes mellitus. Eight of the patients also had coronary atherosclerosis. One patient had previously undergone a unilateral lumbar sympathectomy. Various forms of vasodilator therapy had previously been given to most of the group with little or no improvement. Five patients had been on a strict low fat, low cholesterol diet for at least a year prior to the onset of heparin therapy. The diet was not altered in any patient during this study. Unfortunately observations of blood flow were not made prior to the use of dietary therapy so that we have no objective evaluation of the effect of diet alone, but symptomatically these 5 patients had not improved on the diet. No patient was selected for this study in whom there was a palpable arterial pulse either at the popliteal or ankle level. The oscillometric index below the knee was markedly reduced in all cases. Prior to the onset of therapy, and at irregular inter-

TABLE 1: EFFECT OF INTRAVENOUSLY ADMINISTERED HEPARIN ON S_F 12-100 LIPOPROTEINS (FROM GRAHAM *ET AL.*)

Time after heparin *Pre-heparin*	*Sf 12–20* *(mg/100cc)* *197mg/100cc*	*Sf 20–100* *(mg/100cc)* *357mg/100cc*
70 min.	147	18
3 hours	102	14
4 hours	21	0
6 hours	83	18
24 hours	81	160
72 hours	107	164

vals thereafter, the Lee-White clotting time, blood cholesterol, phospholipid, cholesterol/phospholipid ratio, and the ultracentrifugal analysis of serum lipoproteins was done.*

Heparin** was given in doses of 100 mg. intravenously 2 or 3 times weekly using a 25 or 26 gauge needle. In several cases it was administered daily for the first month. In the 100 mg. per cc. concentration heparin can also be given subcutaneously or intramuscularly, but it is painful to some patients by these routes and may produce a hematoma. During the first few months of therapy the Lee-White coagulation time was determined after each dose of heparin. In all instances the anticoagulant effect persisted for 4 to 7 hours after the injection. The greatest prolongation of clotting time was 60 minutes. Even after 6 months of heparin therapy the clotting times returned to normal within 4 to 7 hours after each dose of heparin. In view of this finding we believe that when heparin is given intermittently in this manner it is not necessary to follow the coagulation times. We have not encountered any serious toxic reactions, nor any hemorrhage. We are aware that some severe anaphylactic reactions have recently occurred elsewhere, but these were due to an impurity in the heparin used. This lot has been withdrawn from the market by the manufacturer.

Method of Study. The 2 most striking manifestations of arterial insufficiency in the lower extremities are intermittent claudication at first, and gangrene finally. The former is a sign of insufficient blood flow to the muscles, while the latter results from inadequate flow to the distal portions of the extremities, especially the digits. Accordingly it seemed logical to test the effectiveness of therapy in 2 ways: by measuring both muscle flow and digital flow. It is well recognized that there is dissociation between the two. For example, vasodilator procedures such as sympathetic block or sympathetic nerve section may produce a huge increase in digital circulation without much change in muscle flow.

The direct measurement of blood flow through muscles is not practical in the living human. However, in an earlier study[2] it had been determined that a level walking tolerance test provides a simple and accurate quantitative measure of changes in the blood supply of the leg muscles. If the subject walks at a given rate along a level corridor until he first feels cramping or other discomfort in his ischemic leg, the distance traversed remains fairly constant in repeated determinations as long as the blood flow to the muscles is unchanged. Neither moderate changes in the environmental temperature nor the emotional state of the patient has any measurable effect on the level walking tolerance. In the present study the observations were made in a long level corridor in which the temperature never went below 72° F. or above 76° F. Each patient was allowed to set his own pace for the initial observation, but the same rate of walking was maintained in all subsequent tests.

The amount of blood flow to the terminal portions of an extremity may be determined by the use of the digital plethysmograph. If the venous outflow is occluded the rate of volume increase of a digit is a direct measure of the rate of arterial inflow[8]. Thus if one knows the actual volume of the digit contained in the cup of the plethysmograph, one can compute the arterial flow in terms of cubic centimeters of blood per unit volume of digit per unit of time. In our observations 5 cc. of digit was used, and the period of venous occlusion was always less than 20 seconds. However, for the sake of convenience, the results have been expressed in cc. of blood/100 cc. of digit/minute. Since digital flow is markedly affected by changes in vasomotor activity, all observations were carried out with the patients at rest in a quiet room at a temperature of 72° to 75° F. A preliminary rest period of 30 to 45 minutes was used for acclimatization to the environmental temperature. None of the patients received vasodilator drugs or heparin for at least 24 hours prior to each observation, and no smoking was allowed for at least one hour before each test. Intrinsic emotional disturbances could not be controlled and undoubtedly introduced some error into the observations. In order to eliminate any error from the presence of spontaneous volume changes described by Burch[4] as alpha, beta and gamma waves, a minimum of 5 readings was made on each patient each time. When large variations due to these spontaneous volume changes seemed to be present an avereage of ten readings was made. All tests were performed by the same observer (T.B.M.).

Results. A. Digital Flow. In 3 extremities the change in digital flow was

*The ultracentrifugal determinations were performed at the Donner Laboratory, University of California, Berkeley, through the courtesy of Dr. John Gofman.

**Supplied by Lederle Laboratories, Inc.

so slight that it was within the limits of accuracy of the method. These were interpreted as "unchanged." In 3 instances there was a very definite decrease in recorded digital flow, but in 2 of these there was a concomitant and rather striking improvement in walking tolerance. The 8 remaining extremities all manifested a significant increase in blood flow to the toes varying from 35 to 400%. With 2 exceptions the increase was over 100%.

Generally the improvement in the peripheral circulation occurred gradually and progressively over the period of observation. In a few cases an increase in flow became apparent within a month, in the others a longer period of therapy was required. During this first 6 months, in those patients in whom the improvement occurred, the walking tolerance steadily increased. By contrast, in 4 extremities there was a greater increase in digital flow after

TABLE 2.—VALUES OBTAINED IN 13 PATIENTS WITH PERIPHERAL ATHEROSCLEROSIS (14 LEGS TESTED) BEFORE AND AFTER HEPARIN THERAPY

Patient	*Age*	*Months of Therapy*	*Chol.*	*S_f 12–20 Lipoproteins*	*Blood Flow in Toe in cc/100cc/min.*			*Walking Tolerance in Feet to Onset of Cramps*	
					Before	*Maximum*	*Last*	*Before*	*Last*
D. B.	67	6	388	71	4.3		4.5	245	243
A. D.	33	4	650	116	Less than 1		2.0	—	—
E. F.	68	4	390	152	1.0		4.0	240	358
D. G.	62	5	345	113	2.4		1.6	328	305
D. G.	30	2	351	104	Less than 1		3.4	364	427
F. G.	72	6	414	59	2.0	6.25	Less than 1	425	525
G. L.	57	6	308	78	2.6		2.2	242	1935
M. N.	63	6	340	62	Less than 1		1.5	220	366
R. R. Symp.	67	4	288	93	4.6	10.9	6.9	—	—
R. L. Unsymp.					Less than 1	3.3	2.3	98	248
L. L.	69	6	415	—	1.8		2.0	—	—
G. R.	55	3	296	—	2.3		6.3	976	1343
W. R.	48	3	415	166	2.8	4.5	3.8	—	—
J. U.	60	6	316	57	6.5		3.4	61	120
C. W.									

B. Muscle Flow. In 4 extremities the walking tolerance test could not be performed. (Cardiac angina was the limiting factor in one patient. In another claudication in the other leg prevented further walking. Two patients had peripheral atherosclerosis, but no claudication.) Of the 10 extremities where muscle flow could be tested 2 remained unchanged on heparin therapy. There were no patients who had any decrease in walking tolerance during the period of treatment. Eight of the 10 patients showed improved walking tolerance varying from 17 to 800%. By comparison with other forms of treatment, such as sympathectomy, there are striking changes.

1 or 2 months of treatment than that observed subsequently. At this time we are unable to explain this finding in view of the steady increase in walking tolerance in 3 of these 4 cases.

Clinically, 11 of our 13 patients had intermittent claudication and 9 of these improved symptomatically. This occurred usually after one to several months of therapy and, in general, paralleled the increases in muscle flow. When therapy was stopped in 4 patients the symptoms recurred in 4 to 8 weeks.

Discussion. Sources of error in plethysmographic measurements have previously been mentioned. While most of these have been to a large ex-

tent eliminated it has not been possible to control the emotional state of the patient and thus prevent emotional vasoconstriction. We have been aware that this would especially apply to the initial measurement in view of the patients' lack of familiarity with the apparatus and the procedure. Therefore, in the initial observation the patients were particularly reassured, longer periods of acclimatization were allowed, and several trial runs were made before the actual measurements were taken. Nevertheless, because of the errors inherent in digital plethysmography, we consider the results of our muscle flow measurements of greater significance than the determinations of digital flow, since muscle flow is influenced slightly, if at all, by emotional factors or other uncontrolled variables. In this regard it is especially significant that the increase in muscle flow following the use of heparin was generally greater than that which one of us (T.B.M.) has observed after lumbar sympathectomy in arteriosclerotic patients. On the other hand, sympathetic block by procaine or surgical section generally produces a considerably greater increase in digital flow than that following heparin. However, from the patient's viewpoint the increase in the ability to walk is the most important result of any therapy, whereas he has very little awareness of the state of digital flow prior to the onset of gangrene.

Table 3 summarizes our results.

TABLE 3.—SUMMARY OF RESULTS: 14 EXTREMITIES, 13 PATIENTS

	Digital Plethysmography	*Walking Tolerance*	*Symptoms**
Improved	8	8	9
Unchanged	3	2	2
Worse	3	0	0

* Two of our patients had no claudication.

MECHANISM OF ACTION. It is not possible (in the light of our present knowledge) to provide a definite explanation of the mode of action of heparin in obliterative atherosclerosis. However, certain possible mechanisms deserve consideration.

1. Anticoagulant effect. We do not feel that this is of primary therapeutic importance in these cases since the anticoagulant action is present for only 4 to 6 hours twice a week.

2. Effects on sludge and viscosity. Laufman[13] has shown that heparin and dicumarol have no effect on sludging. Gilbert and Nalefski[7] have stated that blood viscosity is not altered by heparin or dicumarol.

3. Vasodilator effect. It has been noted by Gilbert and Nalefski[7] and also by Abrahams and Howarth[1] that heparin has a vasodilator action. We do not believe that this effect accounts for the increased flow in our patients. Many had not improved with the use of vasodilator drugs. The increased flow was found 3 to 4 days following the last dose of heparin, and it also occurred in a sympathectomized extremity. The fact that it took several months for improvement to occur argues against vasodilation. One of us has previously shown[5] that there is more improvement in the ballistocardiogram and two-step exercise electrocardiogram 24 hours after heparin than 20 minutes after. The vasodilator effects should be maximal soon after the drug is given intravenously, not the following day. Striking increases in muscle flow are not seen after vasodilator drugs or even after sympathectomy.

4. Improved cardiac output and force. That this may occur after heparin has been objectively shown by the improved ballistocardiogram found in

some cases for 2 to 3 days after a single intravenous dose of heparin[5]. This could result in increased peripheral flow. However, in 2 patients with a progressive, marked increase in digital flow, the ballistocardiogram had been normal prior to the onset of heparin therapy. We do not believe improved cardiac performance is the sole factor in increasing peripheral flow, although it probably is contributory in some cases.

5. Reduction of large serum lipoprotein to smaller molecules of lower S_f rates. This effect always occurs following heparin administration, and the serum lipoproteins return to their former levels in a varying period of time usually in from 24 to 36 hours after the doses we administered. This factor may affect walking ability in several ways:

A. A portion of the serum lipoproteins passes from the blood into the vascular wall[6]. Prior to actually entering the intima, they probably coat the capillary endothelium much like grease on a pane of glass. According to diffusion principles the larger the particles the slower the rate of infiltration. The largest molecules probably remain in the blood stream and would tend to accumulate on the vascular intima. Heparin, just as it clears lipemic sera by conversion of the larger lipoprotein classes into successively smaller ones, probably clears any lipoprotein accumulation on the intimal surface. This might result in improved oxygen exchange through the capillary wall and is a possible explanation of relief of angina or of claudication following heparin. It does not explain increased flow in the digits.

B. That recently developed lesions of atherosclerosis are reversible has recently been shown by Bevans *et al.*[3] in dogs. Katz[12] mentioned reversibility occurring in other animals. Wilens[14] feels the evidence is strong that it occurs in humans. Even temporary reduction of serum lipoproteins would facilitate the possibility of healing recent lesions and reduce the rate of formation of new ones. The delay of several months before improvement occurred in our patients suggests the possibility that healing of more recently developed atherosclerotic lesions was taking place. That some fixed tissue lesions of xanthomatous disease are reversible has been shown by the marked regression of the nodules of xanthoma tuberosum in 4 patients after several months of heparin therapy[9].

It is obvious that much of the above has been speculative. Certainly, however, the present lack of knowledge as to mechanism of action does not negate the improvement observed in our patients. On the basis of these preliminary observations we feel that the intermittent administration of heparin is a promising form of therapy for peripheral atherosclerosis.

Summary. 1. The results in the treatment of peripheral atherosclerosis by the intermittent administration of heparin are presented.

2. Digital plethysmography and level walking tolerance tests were made in 14 extremities.

3. There was significantly improved digital blood flow in 8 of 14 extremities.

4. In 8 of 10 cases there was a marked improvement in level walking tolerance after several months of heparin therapy.

5. Possible mechanisms of action are discussed.

REFERENCES

1. **Abrahams, D. G.,** and **Howarth, S.**: Brit. Heart J., **12**, 429, 1950.
2. **Beaser, S. B.,** and **Massell, T. B.**: New Eng. J. Med., **227**, 43, 1942.
3. **Bevans, M., Davidson, J. D.,** and **Kendall, F. E.**: Arch. Path., **51**, 288, 1951.
4. **Burch, G. E., Cohn, A. E.,** and **Neumann, C.**: Am. J. Physiol., **136**, 433, 1942.
5. **Engelberg, H.**: Am. J. Med. Sci., **224**, 487, 1952.
6. **Evans, S. M., Ihrig, H. K., Means, J. A., Zeit, W.,** and **Hanshalter, E. R.**: Am. J. Clin. Path., **22**, 354, 1952.
7. **Gilbert, N. C.,** and **Nalefski, L. A.**: J. Lab. & Clin. Med., **34**, 797, 1949.
8. **Goetz, R. H.**: Brit. J. Surg., **37**, 25, 146, 1949.
9. **Gofman, J. W.**: Personal communication.
10. **Gofman, J. W., Jones, H. G., Lindgren, F. T., Lyon, T. P., Elliott, H. A.,** and **Strisower, B.**: Circulation, **2**, 161, 1950.
11. **Graham, D. M., Lyon, T. P., Gofman, J. W., Jones, H. B., Yankley, A.,** and **Simonton, J.**: Circulation, **4**, 666, 1951.
12. **Katz, L. N.**: Factors Regulating Blood Pressure, edited by Zweifach, B. W., and Shorr, E. New York, Josiah Macy, Jr. Foundation, 1951, p. 174.
13. **Laufman, H., Govrewski, R., Treger, N. B., Method, H.,** and **Tanturi, C. A.**: Quart. Bull. Northwestern Univ. Med. School, **24**, 257, 1950.
14. **Wilens, S. L.**: Am. J. Path., **23**, 793, 1947.

A STUDY OF MURAL THROMBI ON MYOCARDIAL INFARCTIONS AS A SOURCE OF EMBOLIZATION

By SHIRLEY RUBLER, M.D.

AND

ALFRED A. ANGRIST, M.D.

(From the Queens General Hospital, Jamaica, New York)

THE physician treating a patient with a myocardial infarction is concerned with such complications as ventricular aneurysm, rupture of the myocardium, cardiac failure and recurrent episodes of coronary thrombosis. In addition, further problems arise from embolization, both from the leg veins to the lung, and from the heart to the pulmonary or systemic circulations. Special emphasis has been directed to the role played by mural thrombi over the site of infarction, as the source of such embolic phenomena.

It is of interest to note the incidence in the literature with which mural thrombi have been found over a site of infarction. Wolff and White[12] report that, in 23 cases studied, there were 30% in which mural thrombi formed, while Levine and Brown[7] have noted them in 38 out of 46 cases (83%). Of Meakins' and Eakin's[9] 62 cases, 28 developed this complication, and in the extensive and detailed work done by Bean[2], 47% of 300 cases with infarction had mural thrombi. Nay and Barnes[10] state that the incidence of the formation of mural thrombi in cases of myocardial infarction is 17 to 66%, while Bean[2] found that such thrombi were noted in 34% of a group of cases reported by others. Garvin[6] expressed the opinion that, statistically, mural thrombi seem to occur less frequently in patients with one infarct than in those with more than one. Thus, 61.8% of those with one infarct had mural thrombi, while 86.27% of those with more than one infarction had developed this complication.

It is obvious that statistics on this subject vary markedly. One factor responsible, undoubtedly, for these variations is the degree of care exercised by the investigator. Other factors include the age and extent of the infarct, the physiochemical properties of the blood, and the enzyme factors in the tissues themselves.

The reported rate with which emboli are propagated from mural thrombi again varies markedly with the reviewer. A well controlled study of the embolic phenomenon is a most difficult undertaking. The greatest of all obstacles, perhaps, is the difficulty in distinguishing a thrombus from an embolus.

Of the 300 cases of myocardial infarction studied by Bean[2], 47% had mural thrombi with 78 instances of embolic phenomena occurring in 60 patients. In 12 of these cases, however, sources other than the mural thrombi could have been responsible, that is, leg veins in those with pulmonary infarcts, and thrombotic non-bacterial endocarditis and mural thrombi of the auricles in those with secondary systemic arterial occlusions. Of the occlusions occurring in the systemic circuit, the renal arteries were involved in 20 instances, the splenic in 13, the

cerebral in 6, the femoral in 5, the mesenteric in 2, and the carotid in one.

Nay and Barnes[10] studied 100 cases of myocardial infarction with clinical analyses but, in only 5 of these were the findings substantiated by postmortem examination. It was found that 37% developed either thrombotic or embolic occlusions of the following vessels: 15 recurrent coronary artery thromboses, 14 pulmonary emboli, 8 cerebrovascular thromboses, 7 peripheral venous thromboses and 4 peripheral arterial occlusions. This represents 48 instances of thrombotic or embolic phenomena in 37 patients. No attempt was made to differentiate between these two types of occlusion. Furthermore, some cases had co-existent auricular thrombi. These, rather than the ventricular mural thrombi, may have served as a source of embolization. Subsequent infarctions as well as pulmonary thromboses were included in the general group of thrombi and emboli, thus introducing many extraneous factors. Their cases included 66 males and 24 females with an average age of 57.9 years for the males and 61.9 years for the females.

Of a series of 175 cases with mural thrombi studied by Blumer[3], a total of 35 occlusions in 27 cases were noted. These were in the following vessels: pulmonary veins 16, cerebral arteries 9, renal arteries one, arteries of the extremities 6, and peripheral arteries 3. As in Nay and Barnes' series, the pulmonary veins and the cerebral and peripheral arteries were very frequently involved.

Of Meakins and Eakin's[9] 62 cases of infarction, of which 29 had mural thrombi, instances of embolization were seen in 9 (15%).

Conner and Holt[4], reviewing 287 cases of coronary thrombosis, noted systemic embolic phenomena in 28 instances. They decided that 14 of these were definitely embolic and 2 thrombotic.

In a study of 1000 autopsied cases of cerebral arterial occlusions, Dozzi[5] was impressed by the large number of co-existent myocardial infarctions, which numbered 12 in his series. In only one of the 12, however, could the cerebral occlusion be attributed with certainty to an embolus arising in the heart, while in the other instances it may have resulted from an altered physicochemical state of the blood and general arteriosclerosis, involving all vessels including the brain and heart. He then proceeded to explore the corollary of this, and discovered that, of 41 cases with coronary occlusions, 12, or 29%, had had a cerebrovascular accident. He felt unable, however, to differentiate thrombotic from embolic manifestations.

Parkinson[11], exploring a similar problem found that in 66 cases with hemiplegia, 12.1% (8) had coronary thrombosis, 2 being associated with myocardial infarcts of long standing with mural thrombi, and 2 others being infarcts of recent origin.

The study of the basic cause of mural thrombi is not the object of this paper, nor are we primarily concerned with the reasons why some are dislodged while others remain adherent. It is interesting to note, however, that while mural thrombi occurred in 47% of all the 300 myocardial infarctions reported by Bean[2], such thrombi occurred in 23 out of 31 cases with ventricular aneurysm (74%). As for the incidence of ventricular aneurysm itself, Bean's series disclosed a 16% incidence while Lisa and Ring's[8] was 5% and Appelbaum and Nicolson[1] reported 38%. The earliest appearance of an aneurysm in Bean's series occurred 17 days after infarction, but others have noted aneurysms 6 days post-occlusion.

Another notable observation by

Bean[2] was that in more than one half of all cases with mural thrombi, the septum was the site of this formation. In his opinion, this was a more frequent site of embolization than other locations in the heart.

As for the time required for embolization to occur from mural thrombi, Blumer[3] found that in 60% of his cases the accident took place within 10 days following the occlusion, and in 40% between the 11th and 38th days.

A study of embolic phenomena in myocardial infarction would be inadequate without at least a brief separate consideration of pulmonary embolization. Meakins and Eakin[9] reported that 26 of their 62 cases (42%) developed this complication. In Bean's series[2], 75% of those with right ventricular thrombi had pulmonary embolization. Despite this, however, he was of the opinion that veins of the lower extremities are the major source of *fatal* pulmonary emboli. The mortality from pulmonary embolism was 5% and was noted to range from 3 to 42% before the use of anticoagulants, depending on whether clinical or pathological studies were utilized.

Material. The material for this study was derived from the autopsy and clinical records of cases with postmortem examinations performed by the Pathology Department of Queens General Hospital, Jamaica, Long Island. All the autopsies performed from the years 1936 through 1950 were reviewed, and numbered 8676. Of these, 669 were cases of myocardial infarction. From this group 189 or 28.3%, were selected because they satisfied the following criteria: 1) The existence of coronary occlusion with consequent myocardial infarction. 2) The presence of mural thrombi in either the right or left ventricles or both.

Results. Of the 189 selected cases, 117 (61.9%) were males and 72 (38.1%) were females. The average age of the males was 62.5 years, while that of the females was 65.7 years. The figures quoted here are somewhat higher than those in other studies of coronary disease. We attribute this to the general pool of older individuals from which our autopsy cases were derived. The oldest patient was 87, while the youngest was a female of 35.

The coronary vessel most commonly involved was the left anterior descending artery. This vessel was found to contain a thrombus in 109 cases, whereas the right coronary was occluded in 33 cases. The left main coronary artery was reported to be thrombosed in 9, and the left circumflex in 14 cases.

In 91 instances, only one occlusion was noted, while in 54, 2 arteries were occluded. In only one case were 3 separate occlusions found. The high incidence of single closures, as well as the preponderance of thrombi in the left anterior descending artery, may be explained by the high incidence with which severe sclerosis of all arteries was found. It is possible that some of these arteries might have contained old and fresh thrombi that were obscured by the marked sclerosis. Supporting this opinion are the 42 cases in which no definite occlusions could be found to explain a myocardial infarction. In all these cases sclerosis of the coronary arteries was marked and well established. Injection methods of observing thrombi were not utilized and though multiple transverse incisions across the coronary arteries were closely placed, small thrombi could have escaped the attention of the observer.

In 75 cases, the occlusions were noted to be fresh while in 59 they were old. In 14 cases both fresh and old thrombi were noted in the same artery.

Of the 136 cases in which the exact localization of the infarct was indicated, 30 involved the anterior wall and/or the apex of the left ventricle, and 53 involved the anterior wall and/or the apex plus the interventric-

ular septum. In 16 the posterior wall of the left or right ventricle was involved, while in 13, there was involvement both of the interventricular septum and the posterior wall. The interventricular septum alone was infarcted in 13 instances, and the lateral wall of the left ventricle in 6. In 5 cases the infarct extended through the interventricular septum to involve both the anterior and posterior walls.

Systemic embolic phenomena occurred 69 times in 46 cases. There were sources for emboli other than mural thrombi overlying infarcts in 8 of these. Such alternate sites were non-bacterial thrombotic endocarditis (3 cases) and left auricular thrombi (5 cases).

An attempt was made to correlate the sites of mural thrombi with the incidence of embolization. Mural thrombi which had been responsible for emboli were located as follows: interventricular septum, 23 cases; left ventricle, exact site unspecified, 15 cases; endocardium of the anterior left ventricle or apex, 27 cases; and, right ventricle, on the right side of the interventricular septum, 5 cases. While a high percentage of those thrombi that embolized were situated over the interventricular septum, those of the anterior or apical portions of the left ventricle, contrary to Bean's[2] view, produced emboli with equal frequency. The mural thrombi were fresh in 26 cases, and old, with fresh superimposed thrombus, in 20 cases.

Mural thrombi overlay ventricular aneurysms in 38 cases and produced embolic phenomena from such a site in 11 cases. Embolization, therefore, occurred in 29% of cases with this complication, as compared to 24% for the entire group.

Our study confirms the findings of others that systemic emboli are found most often in the kidney and spleen (37 and 18 respectively in this series). Four were found in the mesenteric arteries, 3 in the adrenals, 2 in the femorals, 2 in the aorta, and one each in the celiac and cerebral arteries. Multiple emboli were frequently encountered and, whereas a single such phenomenon occurred in 25 instances, 2 episodes of embolization were noted in 32 cases, and 3 in 12.

Emboli were distinguished from thrombi by their tendency to resemble the fresher layers of the thrombus from which they were derived, and by their folded configuration which did not generally follow the pattern of the vessel in which they were contained. Emboli were more often localized at the bifurcation of a vessel and these vessels showed no atherosclerotic changes. Thrombi, however, had distinct lines of Zahn and fibrin layers which oriented themselves in relation to the vessel wall. The latter demonstrated secondary syneresis not observed in emboli.

Fifty occlusions occurred in our series which we adjudged due to thrombi, although some may have been caused by emboli. Thirty of these occlusions were found in the cerebral arteries, 10 in the extremities, one in the aorta, and one in the spleen.

Pulmonary emboli were found in 46 cases (26%). A specific source was noted by the prosector in 22 cases and, of these, 10 were found to have originated from a mural thrombus of the right auricle, 7 from the leg veins, 3 from right auricular thrombi or leg veins, one from a mural thrombus in the right ventricle, and one from the prostatic plexus. No presumptive site of origin was found in 24 (approximately 50% of the cases). These probably originated in thrombi located in the veins of the leg (dissections of the leg veins were not done routinely.)

To compute the length of time those patients who developed pulmonary

emboli were confined to bed prior to death, the number of days of hospitalization was used as a criterion because the history of illness at home was vague. It was thus ascertained that the average period of confinement to bed was 22.4 days. The longest period of bed rest was 90 days; the shortest less than 24 hours. These figures would seem to indicate that prolonged immobilization in bed predisposes to pulmonary emboli from the leg veins.

Discussion. The primary purpose of this paper was to consider the importance of mural thrombi as a source for embolization in the convalescent period of patients with myocardial infarctions. The convalescent period at this hospital usually extends for 6 weeks. The incidence, as we found it, was great enough to be of clinical significance.

Our greatest problem was to distinguish truly embolic phenomena from coexisting thrombotic closures. Our series would seem to indicate that the latter phenomenon is of as great clinical significance as the former. Many patients in cardiac failure with concomitant stasis also had coexisting arteriosclerosis of cerebral and femoral vessels. These factors caused a predisposition to multiple thrombi. In addition, these patients may have had an altered physiochemical balance in the clotting mechanism which may have initiated the original coronary thrombosis and continued to cause more thrombi in other vessels. Enzyme disturbances following the destruction of cardiac muscle and further stasis created by bed rest again may have favored independent thrombus formation.

Of the 46 cases with definite embolic phenomena, sources other than mural thrombi were found in 8. Of these, 5 had thrombi in the left auricular appendage and 3 had a non-thrombotic bacterial endocarditis. We concluded, therefore, that 2 sources of emboli may coexist in the same case and that it may be difficult to decide in some instances from which source the emboli actually developed.

Other reports have stated that thrombi over the interventricular septum were a favorite site for embolization. We could not substantiate these findings since our study indicated that emboli occurred with equal frequency from the endocardium of the anterior wall and apex of the heart.

The incidence of ventricular aneurysms in this group was 20.1% (38 cases). Of these, 29% were probable sites of embolization as compared to 24% for the entire group. Although these differences are not of statistical importance, the possibility remains that mechanical factors may favor embolization from mural thrombi located in aneurysmal sites.

Pulmonary emboli were found in 46 of the 189 cases studied. Sites such as the leg veins, right auricle, right ventricle and prostatic plexus were noted to be the source in approximately one-half of the cases. Mural thrombi in the right ventricle were rare and only one instance was found in which such a thrombus could have produced a pulmonary embolus. No source of these emboli could be found in 24 cases and this was presumed to be due to the fact that dissection of the leg veins was not routinely performed in these autopsies. Nevertheless, the veins of the lower extremities were probably the site of origin of the majority of these pulmonary emboli. It was noted that the average period of confinement to bed in these cases was 22.4 days and, therefore, represented a prolonged period of immobilization prior to the occurrence of this complication.

Summary. The incidence of embolization from cardiac mural thrombi was investigated.

1. Of the 189 cases reviewed, there were found 69 instances of probable embolization in 46 patients.

2. Mural thrombi that served as probable sources of emboli were located on the interventricular septum in 23 cases and on the anterior wall or apex of the left ventricle in 27 cases.

3. The kidney and spleen were the most common sites of embolization with 37 such emboli in the kidneys and 18 in the spleen.

4. Other sources from which emboli may have been derived were found in 8 cases (5 had left auricular thrombi and 3 had non-bacterial thrombotic endocarditis).

5. There were 38 ventricular aneurysms amongst the 189 cases (20.1%). Embolic phenomena occurred from 11 thrombi situated in these aneurysms.

6. Forty-six cases with pulmonary emboli were noted and, where the source was known, 10 arose in the right auricle, 7 in the leg veins, 3 in both sites, and 1 in the prostatic bed. In only 1 case was it noted that the embolus may have arisen from the right ventricle.

7. Pulmonary infarcts, the most frequent complication of myocardial infarction, were derived from thrombi more probably situated in the leg veins, and not from mural thrombi in the ventricle.

8. Fifty cases of thrombotic occlusion of systemic arteries other than coronary were noted. These were probably thrombi, but the question remains as to the possibility that some may have been emboli.

9. Many occlusions accepted as embolic actually represent thrombosis *in situ* in individuals with an altered intravascular clotting mechanism.

10. Mural thrombi represent a significant source of embolization in patients with myocardial infarctions.

REFERENCES

1. **Appelbaum, E.,** and **Nicolson, G. H. B.:** Am. Heart J., **10,** 667, 1935.
2. **Bean, W. B.:** Ann. Int. Med., **12,** 71, 1938.
3. **Blumer, G.:** Ann. Int. Med., **11,** 499, 1937.
4. **Conner, L. A.,** and **Holt, E.:** Am. Heart J., **5,** 705, 1930.
5. **Dozzi, D. L.:** Ann. Int. Med., **12,** 1991, 1939.
6. **Garvin, C. F.:** Am. Heart J., **21,** 713, 1941.
7. **Levine, S. A.,** and **Brown, C. L.:** Medicine, **8,** 245, 1929.
8. **Lisa, J. R.,** and **Ring, A.:** Arch. Int. Med., **50,** 131, 1932.
9. **Meakins, J. C.,** and **Eakin, W. W.:** Canad. Med. Assn. J., **26,** 18, 1932.
10. **Nay, R. M.,** and **Barnes, A. R.:** Am. Heart J., **30,** 65, 1945.
11. **Parkinson, J.,** and **Bedford, D. E.:** Lancet, **1,** 4, 1928.
12. **Wolff, L.,** and **White, P. D.:** Boston Med. & Surg. J., **195,** 13, 1926.

EVALUATION OF AMODIAQUIN (CAMOQUIN) IN THE TREATMENT OF RELAPSING VIVAX MALARIA

By JULIAN LOVE, M.D.
CAPTAIN, MC, U. S. NAVY

RICHARD FOULK, M.D.
LIEUTENANT, MC, U. S. NAVY

ROBERT G. W. WILLIAMS, JR. M.D.
LIEUTENANT, MC, U. S. NAVY

AND

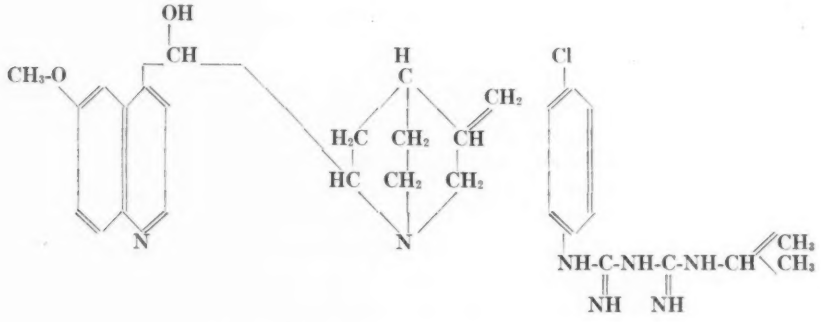
RONALD B. MITCHELL, M.D.
LIEUTENANT (jg), MC, U. S. NAVAL RESERVE*

(From the U. S. Naval Hospital, Philadelphia, Pennsylvania)

THE urgency of the malaria problem at the inception of World War II intensified by the disruption of the supply of quinine from the Dutch East Indies led to intensive anti-malaria drug investigation. At first only those substances which on preliminary evaluation had seemed most promising were fully explored and utilized. Thousands of chemical compounds were tested and from these a few with undeniable therapeutic effects were obtained. These included the 4-aminoquinoline drugs such as chloroquin, the 8-aminoquinoline drugs derived from Pamaquin such as pentaquin and primaquin, and the British-developed benzene-ring compound, Paludrine.

It is not surprising that other equally or more efficacious drugs were bypassed because the results obtained in initial experiments were not so favorable as those with the above-mentioned drugs. Among these was amodiaquin, a 4-aminoquinoline compound.

Amodiaquin originally was known as

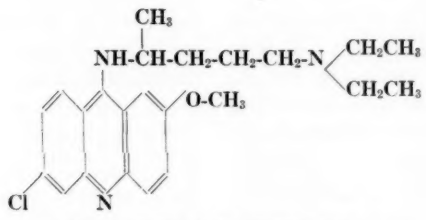


QUININE

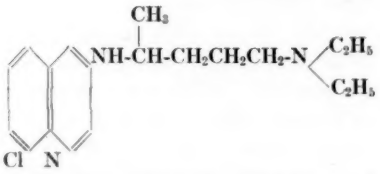
CHLORGUANIDE (PALUDRINE)
N_1-p-Chorophenyl-N_5-Isopropyl Biguanide Hydrochloride

FIG. 1a.—Chemical and Structural Formulae of Quinine and Chlorguanide (Paludrine).

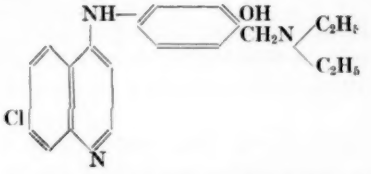
*The opinions expressed in this article are those of the authors and do not reflect the official opinions of the Bureau of Medicine and Surgery or the U. S. Navy Department.



QUINACRIN (ATABRIN) SN 390
2-Methoxy-6-Chlor-9-(A-Methyl-8-Diethylamino Butyl)
Amino Acridine

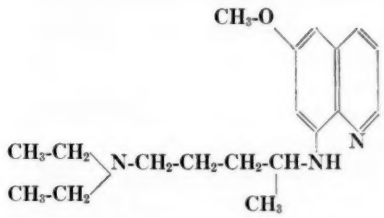


CHLOROQUIN (ARALEN) SN 7618
7-Chloro-4(4-Diethylamine-1-Methyl-
Butylamine) Quinoline

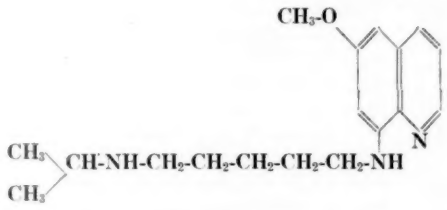


AMODIAQUIN (CAMOQUIN) SN 10,751
4(3'-Diethylaminomethyl-4'-Hydro-
Xylamino-7-) Chloroquinoline

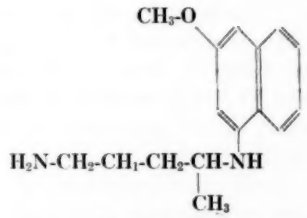
FIG. 1*b*.—Chemical and Structural Formulae of Quinacrin (Atabrin), and the 4-aminoquinolines, Chloroquin and Camoquin. Note that Quinacrin Synthetic Number 390 Differs From Chloroquin Synthetic Number 7618 Only by an Additional Methoxybenzene Radicle.



PLASMOCHIN (PAMAQUIN)
6 Methoxy-8-(A-Methyl-8-Diethylaminobutyl)
Amino Quinoline



PENTAQUIN SN 13276
7-Methoxy-8-(5-Isopropyl-Amino-
Aminylamino) Quinoline



PRIMAQUIN SN 13272
8-(4-Amino-1-Methybutlyamino)-
6-Methoxyquinoline

FIG. 1*c*.—Structural and Chemical Formulae of the 8-aminoquinolines, Plasmochin, Pentaquin, and Primaquin.

SN 10,751, and later, as Cam AQ1, miaquin, but now most familiarly, as Camoquin. Chemically, it is 4 (3′ diethyl aminomethyl-4′-hydroxyanilino) 7 chloroquinoline dihydrochloride dehydrate. The chemical relationships and structural formulae of quinine, quinacrine, chloroquin, Camoquin, Pamaquin, pentaquin, primaquin, and Paludrine are shown in Fig. 1a, 1b, and 1c. The most recent anti-malarial drug advocated by the British is daraprim[13] (2:4-diamino-5-p-chlorophenyl-6-ethyl primidine) whose action parallels that of paludrine, but is considered more effective.

Amodiaquin was first synthesized in 1946 by Burckhalter *et al.*[2] It is an orange-yellow crystalline powder and is supplied as the dihydrochloride dehydrate. The drug* is supplied commercially in 200-mg. scored tablets. It also may be made into a 5% solution for parenteral administration.

The experiments of Parke-Davis Company revealed that Camoquin HCL is absorbed rapidly from the gastrointestinal tract, and an adequate blood concentration is obtained one hour after oral administration. The drug is unequally distributed in body tissues and is most highly concentrated in the spleen and liver. The concentration in the red blood cells is double that found in the plasma. Animal experiments have shown that definite amounts of Camoquin persist in the tissues a week or longer after a single dose. The compound is excreted in its original form in very small amounts, less than 5% being excreted in the urine and feces. The remainder is metabolized in the body.

The toxic manifestations of Camoquin are considered practically insignificant and have been reported by various authors to include transient mild nausea, vomiting, headache, diarrhea, and a few other minor complaints. It rarely, if ever, causes staining of the skin or tissues. Coggeshall[5], after a pharmacologic study with 2000 men, concluded that Camoquin was less toxic than chloroquin.

Clinical trials in India[18], the Philippines[7], Egypt[8], Panama[10], and Brazil[14], have shown uniformly good results. Dosages ranging from 0.5 gm. in one single dose to 0.5 gm., 3 times daily for 2 or 3 days have been employed. The dose currently recommended is a single one of 10 mg./kilo body weight. The drug has been used in the presence of pregnancy, cirrhosis, nephritis, and nephrosis with no ill effects. The relapse rates, thus far reported[7,8,9,10,14,18,21] have varied from 0%[18] to 12%[14].

Numerous investigators[7,8,9,10,14,18] have used Camoquin in *Plasmodium falciparum* infestation with very good results. Fever disappeared in 5 days, and parasites could not be found after 4 days in one study[7]. Parasitemia vanished in an average of 29.2 hours in another study[9]. The drug is effective on both gametocytes and schizonts in vivax malaria and is rapidly lethal to the schizonts of falciparum malaria but only slowly so to the gametes. The 8-aminoquinolines may be required to rid the blood of these forms. Chaudhuri *et al.*[4] have found that Camoquin, in weekly doses of 100 or 200 mg., is comparable to chloroquin in the chemoprophylaxis of malaria.

Method. This study is based on the treatment of 100 consecutive patients with relapsing *Plasmodium vivax* malaria at the U. S. Naval Hospital, Philadelphia, Pa., admitted from November, 1950, to December, 1951. Our statistical conclusions are based upon follow-up observations to July 1, 1952. Almost all of the cases in this series were members of the armed forces who had recently returned from the Korean theatre of operation. The time interval between leaving Korea and onset of the first malaria symptoms had a wide variation; the shortest time interval being 2 weeks and the longest being 11 months.

*Supplied through the courtesy of Parke-Davis Company.

Approximately 75% of these patients received suppressive therapy with 0.5 gm. of chloroquin once weekly while in the malarial zone. However, many of the patients were unable to take the drug at the recommended interval, due either to the exigencies of their duties or to their own neglect. Twelve per cent of this group gave a history of having had previous malarial attacks which were treated with chloroquin or by other antimalarial drugs. An average of 5.36 months elapsed since the previous attack in this group, with the shortest and longest intervals being one month and 12 months respectively.

Ralph Jones[11] has reminded us of a characteristic of vivax malaria which was well known to malariologists and practitioners of many years ago. They recognized that frequently there occurred a long latency period of several months between an original attack of malaria and its initial relapse. This is an adaptive mechanism of the organism to permit its sexual forms to appear in the peripheral blood of a human at the time when Anopheline mosquitoes are again present in the environment. It is felt that this mechanism applies to those where initial clinical break through occurred months after their return to the United States.

The majority of our patients developed symptoms within a week or a few days prior to admission. The predominant complaints were those of intermittent high fever,

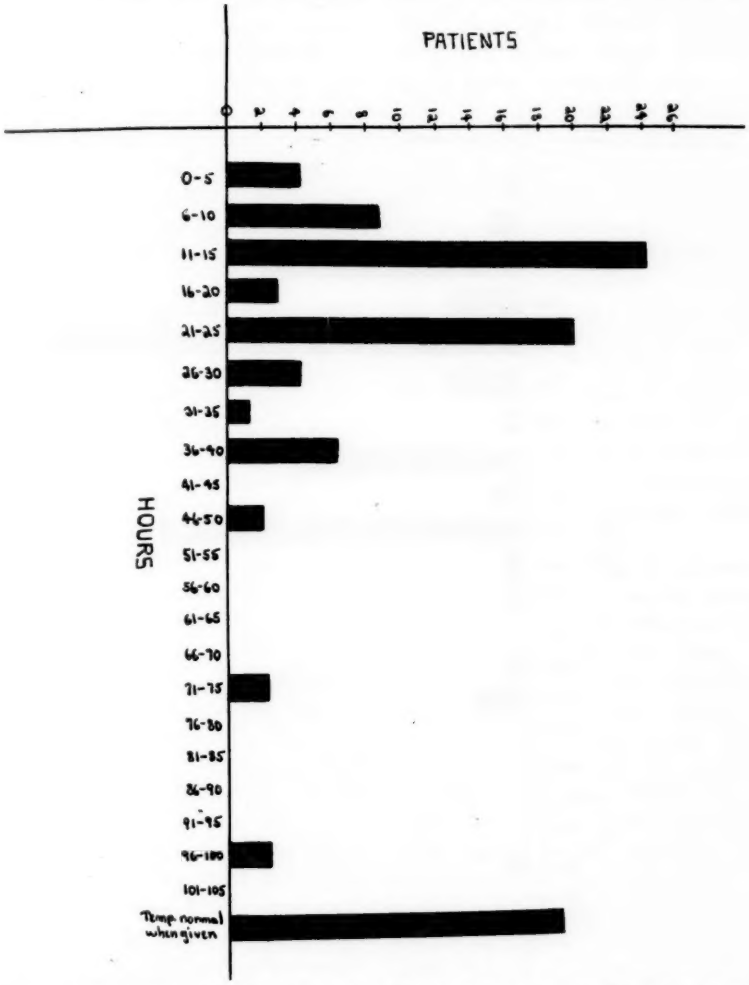


FIG. 2.—Temperature response after the ingestion of a single dose of 10 mg./Kilo of body weight of Camoquin.

chills, malaise, headache and anorexia. Many also complained of nausea and vomiting. Physical examination for the most part was essentially negative except for splenomegaly which was present in 34% and pharyngitis in 20% of patients. Hepatomegaly, herpes labialis, bronchitis, and lymphadenopathy were also present in a small percentage of patients.

Laboratory studies revealed a moderate anemia in 32% of the cases. Leukopenia and lymphocytosis were present in 30% and 29% respectively. Eosinophilia and monocytosis were found in 7% and 31% respectively. A positive blood Kahn was present in 13%. Stool examinations for ova and parasites were done on 50 cases of this group. Eight of these, representing 16%, were found to have *Ascaris lumbricoides* infestation. Only one case was found to have hookworm. No other parasitic infestations were noted.

When malaria was suspected because of the presenting symptom complex, the following regimen was adopted. Thick and thin malaria smears were taken from each patient. If the smear was positive for *Plasmodium vivax*, the patient was admitted to the hospital and transferred to a ward in which all malaria cases were treated. Intercurrent relapse malaria was discovered in some of the patients who were in the hospital being treated for other conditions. These were brought to our attention and followed by

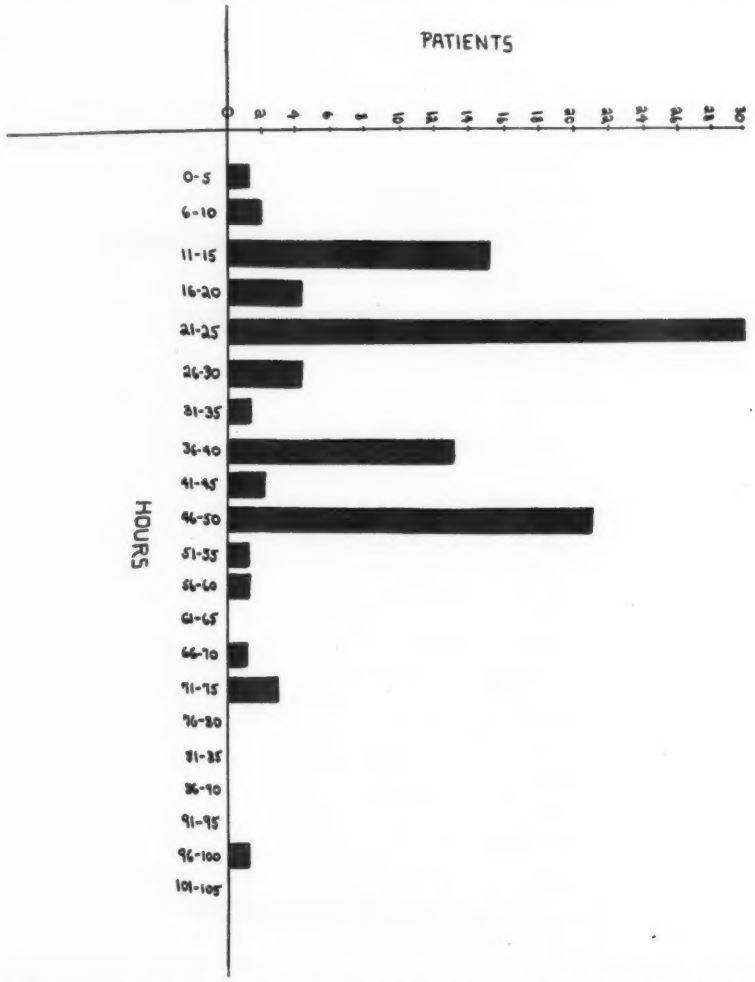


FIG. 3.—Disappearance time of parasitemia following the ingestion of a single dose of 10 mg./kilo of body weight of Camoquin.

us during their hospital stay on other wards.

The temperature was taken 4 times daily; blood smears (thick and thin) were taken 2 times daily at 8 A.M. and 8 P.M. until 2 consecutive days of negative smears were obtained. These smears were read by the doctors conducting the study. Additional laboratory studies including urinalysis, complete blood count, Kahn and Kolmer, a stool examination, and any other tests that were warranted were performed.

When the diagnosis was established, a single dose of Camoquin of 10 mg./kilo body weight was given. In the majority of cases this ranged from 600 to 800 mg. or 3 to 4 tablets.

Results. The fever had a rapid return to normal in all but a few cases. If Camoquin was given immediately prior to an anticipated paroxysm, fever would develop, but only for that elevation. No other paroxysms followed. If the drug was given shortly after a given paroxysm, the occurrence of temperature elevation was exceptional. These observations are essentially the same as those of other investigators[7,8,14,18].

Concurrent with this drop or diminution of fever, marked subjective improvement in the patient was noted. In patients who had fever, the average time for the temperature to return to normal was 18.6 hours. No fever was present in 20% of our patients at the time Camoquin was given, and no fever followed administration of the drug except in the one patient who had a concurrent lobar pneumonia. The longest time taken for the temperature to return to normal was 96 hours. Other groups have reported a return of temperature to normal at an average of 15.8 hours[14], and 28 hours[18]. Figure 2 reveals that (24.5%) of the cases had a normal temperature within 11 to 15 hours.

The average number of hours taken for the parasites to disappear from the peripheral blood was 29.91 hours. If blood smears had been taken more frequently than every 12 hours, this average time would have been reduced considerably. The most rapid disappearance of parasitemia in this series was 10 hours, whereas persistence of parasitemia was found in some cases up to 72 hours after administration of the drug. It should be noted in Figure 3 that the greatest percentage of patients (30%) had negative blood smears in the period between 21 to 25 hours following administration of Camoquin. This figure is slightly higher than those noted by other authors[9,14,18]. In several cases the interscapular method of Van den Berghe *et al.*[20] was used while checking for parasitemia, but we feel no advantage is offered by this method over peripheral blood smears in the acute cases of malaria.

Of the 100 patients treated in this series, twenty (20%) relapsed. This represents the first relapse. Three relapsed a second time (3%) and one a third and fourth time. Although all patients at the time of their discharge from this hospital were requested to notify us by mail of any future relapse, we may not have been notified in all cases. At this time at least 7 months have elapsed since the last patient of this series was treated with Camoquin, but more patients may yet relapse. Because of these 2 factors, the ultimate relapse rate may be a little higher than our present figures indicate.

The average time of occurrence of the first relapse was approximately 49.6 days. The earliest relapses occurred after 26 days, and the latest reported to date was 150 days following treatment. Ejercito *et al.*[7] using approximately one-half our usual dosage reported 6 relapses out of 44 cases in an average of 30 days. However, the majority of authors give a very low relapse rate, or no relapses, using 10 mg./kilo dosage or higher[7,9,10,14,18]. The average time of the second relapse which occurred in 3 patients was 39 days, the earliest on the 17th day and the latest on the 62nd day. There was

one patient who had 4 relapses. To our knowledge this is the first reported case having a third and fourth relapse following Camoquin therapy in this dosage. This latter relapse occurred despite an increase in dosage to 15 mg./kilo body weight, indicating that little will be gained by increased dosage. This particular patient sustained severe multiple injuries while in Korea, and this fact may well have contributed to lower resistance to account for these relapses. An average of 11 months has passed since therapy of those patients who have not relapsed.

Other than mild nausea and vomiting in only 6 of our patients (6%), no toxicity was noted after the administration of Camoquin. This apparent low toxicity to the drug is in accord with the reports of all other authors. Parenteral Camoquin was not used in this series but has been used successfully by Payne *et al.*[16,17] in cases who were unable to take the drug orally. However, because of protracted nausea and vomiting associated with his malaria, one patient in this series was given the indicated oral dose by insertion of the tablets rectally. He had a similar clinical response to those taking the drug orally and to our knowledge has not relapsed. There were no evidences of any untoward local reaction to the drug.

Although the literature reported little or no toxicity from Camoquin in this dosage, higher dosage may have a serious toxic effect. A few patients with Boeck's sarcoid have been treated at the U. S. Naval Hospital, Philadelphia, by exhibition of 600 to 700 mg. of the drug every fourth day for one month. In 2 of these patients leukopenia developed. On discontinuation of the drug and with supportive therapy, however, the white blood count returned to normal.

The current drug of choice for the treatment of *Plasmodium vivax* malaria is chloroquin diphosphate. This is a white crystalline substance which is commercially available in tablets of 0.25 gm. The total dose of this drug for the treatment of an acute attack of malaria in adults is 2.5 gm. (10 tablets) given over a 3-day period, in contrast to the single dose with Camoquin. This regimen is sufficient to eradicate infestation due to *Plasmodium falciparum* and terminate the acute attack of *Plasmodium vivax* malaria. Effective suppression of malaria can be attained with a single weekly dose of 0.5 gm. (2 tablets) of chloroquin diphosphate[15]. Chloroquin diphosphate is now available in 0.5 gm. tablets. This drug has no major toxic manifestations although pruritus has occurred in some patients following a course of the drug. The series of cases showed a 70% relapse rate, the average time interval being 60 days between episodes.

Within the past months primaquin SN 13272, an 8-aminoquinoline, has been given to all troops returning from Korea since preliminary studies indicated that when given in 15 mg. dosage daily for 14 days a 99% cure rate was obtained with no serious toxicity. In the past 6 months, since the above regimen has been in effect, there have been no patients admitted to this hospital with malaria of recent Korean origin who have received primaquin, indicating the effectiveness of this new preparation.

Summary. One hundred consecutive patients with relapsing *Plasmodium vivax* malaria were treated, with Camoquin, a 4-aminoquinoline compound. All clinical symptoms were controlled in 24 to 48 hours, temperature returned to normal on an average of 22.5 hours, and parasitemia disappeared in 30 hours in the first attack, in 21.5 hours in second relapses.

Relatively few toxic reactions were noted to Camoquin in the recommended single dose of 10 mg./kilo body weight. In a few patients with Boeck's sarcoid given the above dosage every

4 days, leukopenia occurred but recovery ensued when the drug was discontinued.

Up to July 1, 1952, the relapse rate is 20%. At least 7 months has elapsed since the last patient in this series was treated. Three per cent of patients relapsed twice and one patient has had a third and fourth relapse, the last one occurring despite treatment with 15 mg./kilo body weight.

Conclusions. 1. Camoquin given in a single dose of 10 mg./kilo body weight is an effective anti-malarial drug, but in this series had a 20% relapse rate. Higher dosage of the drug should be used with caution due to the possibility of leukopenia. Camoquin may be used parenterally and rectally with no apparent ill effect. It has been successfully used for the chemoprophylaxis of malaria.

2. Camoquin has the advantage over chloroquin in being effective in a single dose. This fact is very important, especially in war, and when treating ambulatory patients in areas where malaria is more prevalent.

3. Chloroquin in 0.5 gm. dosage once weekly is the best drug for suppression but when used therapeutically in 2.5 gm. dosage over a 3-day period has a much higher relapse rate than a single dose of Camoquin.

4. Preliminary impressions are that primaquin[6,11] in 15 mg. dosage for 14 days is by far the most effective curative anti-malarial drug.

5. The recommended treatment of an acute attack of *Plasmodium vivax* malaria at present is a single dose of Camoquin 10 mg./kilo body weight, or 2.5 gm. of chloroquin over a 3 day period, plus a course of 15 mg. of primaquin daily for 14 days to prevent relapses.

REFERENCES

1. Aralan Diphosphate: Booklet published by Winthrop, Stearns, Inc.
2. **Burckhalter, J. H., Pendic, F. H., Jones, E. M., Jones, P. A., Holcomb, W. F., and Rawlins, A. C.:** J. Am. Chem. Soc., **70,** 1363, 1948.
3. Camoquin Hydrochloride: Booklet published by Parke-Davis & Co.
4. **Chaudhuri, R. N., Chakraverty, N. K.,** and **Chaudhuri, M. N. R.:** British Med. J., **1,** 568, 1952.
5. **Coggeshall, L. T.:** Private communication to Dr. Mark T. Hoekenga.
6. **Edgcomb, J. H., Arnold, J., Yount, E. H., Alving, A. S., Eichelberger, J., Jeffery, G. M., Eyles, D. E.,** and **Young, M. D.:** J. National Malarial Soc., **9,** 285, 1950.
7. **Ejercito, A.,** and **Duque, M.:** J. Philippines Med. Assn., **24,** 33, 1948.
8. **Halawani, A., Baz, I.,** and **Markas, F.:** J. Royal Egyptian Med. Assn., **30,** 99, 1947.
9. **Hoekenga, M. T.:** Am. J. Trop. Med., **31,** 139, 1951.
10. Idem: Ibid., **30,** 63, 1950.
11. **Jones, Ralph:** Personal communication.
12. **Loeb, R. F., Clark, W. M., Coatney, G. R., Coggeshall, L. T., Dieuaide, F. R., Dochez, A. R., Hakansson, E. G., Marshall, E. K., Jr., Manuel, C. S., McCoy, O. R., Sapero, J. J., Sebrell, W. H., Shannon, J. A.,** and **Carden, G. A., Jr.:** J. Am. Med. Assn., **130,** 1069, 1946.
13. **McGregor, I. A.,** and **Smith, D. A.:** British Med. J., **1,** 568, 1952.
14. **Mein, R. M.:** Am. J. Trop. Med., **31,** 212, 1951.
15. **Most, H., Londin, I. M., Kane, C. A., Lavietti, P. H., Schroeder, E. F.,** and **Hayman, J. M., Jr.:** J. Am. Med. Assn., **131,** 963, 1946.
16. **Payne, E. H., Sharp, E. A.,** and **Nickel, K. C.:** Am. J. Trop. Med., **29,** 353, 1949.
17. **Payne, E. H., Villarejos, V. M., Sharp, E. A., Reinertson, J. W.,** and **Wille, W. S.:** Ibid., 31, 703, 1951.
18. **Simeons, A. T. W.,** and **Chhatre, K. D.:** Indian Med. Gazette, **82,** 255, 1947.
19. **Thompson, P. E.:** J. Infect. Dis., **83,** 250, 1948.
20. **Van den Berghe, L.,** and **Chardome, M.:** Am. J. Trop. Med., **31,** 411, 1951.
21. **Villarejos, M.:** Ibid., **31,** 703, 1951.

THE CAUSE OF ACUTE PERICARDITIS

By ROBERT L. REEVES, M.D.*

(From the Department of Internal Medicine, St. Luke's Hospital, New York, New York)

A REVIEW of the recent literature reveals a plethora of papers on the subject of acute benign non-specific pericarditis[6,7,8,10,11,12,13,18,22,23,25,31,34,39], but few attempts have been made to establish the incidence of the various causes of acute pericarditis since the work of Preble [32] in 1901. The papers which include such attempts[5,9,29,30,33,35,36,38] are based on autopsy or electrocardiographic reviews or are done on military personnel, and thus are not entirely valid. This study is not limited by the outcome of the disease or electrocardiographic findings, and it represents a cross section of the population, inasmuch as it is based on the charts of all admissions to a general hospital which were diagnosed as acute pericarditis.

Purpose. It is the purpose of this paper to approximate the incidence of the various causes of acute pericarditis. More than likely the paucity of such reports in the literature is in part due to the many possible sources of error involved. However, by reviewing the material carefully and recognizing that the end result is, at best, an approximation, it is hoped that this study will contribute to the concept of the disease.

Method. The chart of every patient on whom the diagnosis of pericarditis was made at St. Luke's Hospital in New York City between the years of 1935 and 1950 inclusive was reviewed (total 129). The criteria set up for the diagnosis of acute pericarditis were classified as (1) unequivocal, (2) major, and (3) minor, and were as follows:

TABLE 1—CRITERIA FOR THE DIAGNOSIS OF ACUTE PERICARDITIS

(1) *Unequivocal*
- (a) Autopsy proof
- (b) Pericardicentesis (or open drainage) with recovery of pathologic fluid

(2) *Major*
- (a) Pericardial friction rub
- (b) Electrocardiographic changes considered as typical of acute pericarditis[28,41]; that is, an elevation of the RS-T segment with an upwardly concave or straight ascending limb in at least 2 of the standard limb leads (preferably 3) in the absence of abnormal Q waves or reciprocal S-T depressions.
- (c) Typical roentgenographic or fluoroscopic findings of pericardial effusion; that is, cardiomegaly affecting the right side of the heart as well as the left ("water bottle configuration") and a diminution of excursion during cardiac cycle.

(3) *Minor*
- (a) Typical physical findings of pericardial effusion excluding the rub; that is, Ewart's sign or merely enlargement to the left and right and distant cardiac sounds.
- (b) Typical history of pericardial involvement; that is, precordial sticking pain accentuated by deep breathing, movement of the torso, and frequently by swallowing, and diminished on assuming the sitting position.

In order to be diagnosed acute pericarditis the charts had to fulfill (a) one of the unequivocal criteria, or (b) 2 major criteria, or (c) one major and the 2 minor criteria. The diagnoses of acute pericarditis made in this way numbered 108 during this 16-year period.

*Present address: The Mason Clinic, Seattle 1, Washington.

An attempt was then made to break the diagnoses down further with respect to the cause involved in each individual case. Again sources of error existed, but to minimize erroneous diagnoses, cases in which the diagnosis was questionable were placed in a separate category of "uncertain cause." Such a category should not give rise to a significant error in actual incidence inasmuch as there will always exist cases of acute pericarditis which do not follow any typical pattern.

The classification used here is one similar to those proposed by Harrison and Resnick[21] and Camp and Clarke[10]. It divides the cases of acute pericarditis into 3 main categories with subdivisions as shown.

TABLE 2.—CLASSIFICATION OF ACUTE PERICARDITIS

I. *Infectious*
- A. Rheumatic
- B. Bacterial
  1. Pyogenic
  2. Tuberculous
- C. Benign Non-Specific

II. *Non-Infectious*
- A. Uremic
- B. Neoplastic
- C. Ischemic

III. *Uncertain Cause*
- A. Collagen Group
  1. Lupus erythematosus
  2. Polyarteritis nodosa
  3. Rheumatoid arthritis
- B. Miscellaneous
  1. Cholesterol pericarditis
  2. No diagnosis made

The diagnosis of acute pericarditis was established first and then a breakdown was accomplished by adhering to the following criteria.

Rheumatic pericarditis was diagnosed in those cases having: (a) a history of a previous attack or attacks of acute rheumatic fever in addition to a history and physical signs indicative of an acute exacerbation or (b) physical signs of rheumatic heart disease in a young person without any other satisfactory explanation, that is, signs of mitral valvular disease and/or aortic valvular disease[16]; or (c) the development of definite evidence of valvular heart disease while hospitalized.

Pyogenic pericarditis was diagnosed either by autopsy (14 cases), thoracotomy with biopsy (1 case), or when a patient developed signs of pericarditis in the face of an overwhelming infection within the thoracic cage or in the blood stream without evidence of any of the other possible causes of pericarditis described here (4 cases).

Tuberculous pericarditis was diagnosed by (a) autopsy (2 cases), (b) a history suggestive of systemic tuberculosis with weight loss, night sweats, weakness, in addition to a long and unsatisfactory hospital course of "painless pericarditis" without response to antibiotics other than streptomycin, and with a persistently elevated venous pressure (1 case), (c) a course and findings similar to (b) with a follow-up revealing proven active tuberculosis (2 cases) or the development of constrictive pericarditis on follow-up (2 cases). An unsuccessful attempt was made to recover the tubercle bacillus by pericardicentesis in only 2 of these cases.

Benign non-specific pericarditis was a diagnosis a little more difficult to make in this type of study. It usually followed or accompanied an upper respiratory infection and was characterized by mild to severe precordial or substernal pain, usually aggravated by breathing and coughing and not infrequently by swallowing. Fever was usually present early in the course. Recovery was complete despite occasional relapses. This type of course, when coupled with the exclusion of all other specific forms of acute pericarditis, called for the diagnosis of the benign non-specific type.

Acute pericarditis was classified as uremic when it existed in the face of severe renal disease and a markedly elevated blood urea nitrogen (over 50 mg. per 100 cc.) All but two of these particular cases were confirmed by autopsy. It is important to note that in the cases with the lower blood urea nitrogen levels (50 to 100 mg. per 100 cc.) a period of time usually elapsed between the last urea nitrogen determination and the development of pericarditis.

Neoplastic invasion of the pericardium with pericarditis was a diagnosis made only by autopsy or biopsy performed during a thoracotomy.

Ischemic pericarditis was diagnosed by the clinical course and laboratory findings in addition to electrocardiographic changes typical of a myocardial infarct. However, the

charts of patients presenting a classical ischemic pericarditis were dropped from this series in the final analysis because the accuracy of the figures on the incidence of ischemic pericarditis in such a series is very questionable. Undoubtedly many cases of myocardial infarction are accompanied by pericarditis which involves such a small area and/or results in a friction rub for such a short period that they are missed by the clinician. Also, it is more than likely that the diagnosis of pericarditis is not recorded on the face sheet of the charts of many patients who were observed to have pericardial friction rubs with myocardial infarcts.

Pericarditis has been described as accompanying certain collagen diseases including rheumatoid arthritis[23]. In these cases, when the primary disease was unequivocally established and pericarditis existed concomitantly without any other known cause, the latter was assumed to be secondary to the collagen disease.

In the miscellaneous group were placed a case of cholesterol pericarditis proved by biopsy[1], and several cases in which the diagnosis of acute pericarditis was established but could not be classified as to cause.

Results. During the 16-year period between the years 1935 and 1950 inclusive a total of 143,115 patients were admitted to all services of St. Luke's Hospital, a general hospital in the City of New York. Of these, 0.07%, or 108 cases, were diagnosed as acute pericarditis.

Twelve of these were diagnosed as ischemic pericarditis and were eliminated from the series. The 96 remaining patients were classified as follows:

TABLE 3.—INCIDENCE OF THE CAUSES OF ACUTE PERICARDITIS

	No. of Cases	*Percentage*
I. *Infectious*		
A. Rheumatic	39	40.6%
B. Bacterial		
1. Pyogenic	19	19.8%
2. Tuberculous	7	7.3%
C. Benign Non-Specific	10	10.4%
II. *Non-Infectious*		
A. Uremic	11	11.5%
B. Neoplastic	3	3.1%
C. Ischemic	12 (not included in series)	
III. *Uncertain*		
A. Collagen Group	2	2.1%
B. Miscellaneous	5	5.2%
TOTAL	96	100.0%

Discussion. The results of this study are not in complete accord with other reviews of the same disease[9,32,36]. This is probably because the above statistics are based on a cross section of the population of a large city and are not limited by the ultimate outcome of the disease or electrocardiographic findings in each case as are autopsy and electrocardiographic reviews. In addition the advent of antibiotic drugs has undoubtedly reduced the incidence of pyogenic pericarditis in recent years.

A number of authors have commented on the higher incidence of the disease in the male, giving ratios as high as 3:1, male to female[5,26,32,33,43]. We find that the ratio of male to female in this series was approximately 3:2. No attempt has been made to explain the male preponderance.

The age group most commonly affected by this disorder was, as previously reported[44], the 10 to 40-year group except when the etiologic agent was a pyogenic organism or uremia. Pyogenic pericarditis more commonly affected the very young or the older age groups. The cases of uremic pericarditis were most frequently seen in the middle age group (40 to 59 years).

The presenting complaints of patients with acute pericarditis were of some interest, though sometimes multiple, and occasionally unrelated to the primary disease. Patients in the rheumatic and pyogenic groups complained most frequently of fever, chest pain, and dyspnea. Many rheumatic patients also complained of joint pains. In the tuberculous class complaints such as cough, weakness, and epigastric pains were quite common, whereas only one of these patients complained of chest

pain. In the benign non-specific category, all of the patients, with one exception, stated that they had chest pain. Most of the complaints presented by those who developed uremic pericarditis seemed to be totally unrelated to the pericarditis.

Of the laboratory findings, the leukocyte count was found to be elevated over 10,000 in the majority of the cases except in the category of tuberculous pericarditis. The highest white blood cell counts were found in the pyogenic group where they ranged up to 54,000 per c. mm. It is of interest to note that 56% of the cases of rheumatic pericarditis had leukocyte counts over 15,000 per c. mm. whereas only 2 cases (20%) of the benign non-specific cases had counts over 15,000 per c. mm.

The electrocardiograms were interpreted as being "suggestive or typical" of acute pericarditis in only 38% of the cases in which they were taken (33 out of 89 cases). Of 32 autopsy-proven cases on whom electrocardiograms were taken, only seven (22%) had electrocardiographic findings considered as "suggestive or typical" of acute pericarditis.

A roentgenogram of the chest was reported as "compatible" with the diagnosis of pericarditis in over half the cases with tuberculous pericarditis, but in only about a third of the cases with rheumatic and non-specific pericarditis. Pleural effusion was reported on the Roentgen-ray report more commonly in tuberculous pericarditis than in the other forms. Pulmonary infiltration was more common in cases with pyogenic pericarditis, and, to a lesser extent, in cases with benign pericarditis.

A pericardial friction rub was heard more consistently in rheumatic pericarditis than any of the other forms (93%). It was heard in well over 50% of all the other types of acute pericarditis except for the pyogenic type.

TABLE 4.—AGE DISTRIBUTION OF ACUTE PERICARDITIS

Age	*Rheumatic*	*Pyogenic*	*Tuberculosis*	*Non-Specific*	*Uremic*	*Neoplastic*	*Collagen*	*Total*
0–9	6 (15.0%)	3 (15%)	1 (14%)	0	1 (9%)	0	0	11 (12.1%)
10–39	24 (62.5%)	2 (10%)	4 (58%)	5 (50%)	2 (18%)	3 (100%)	2 (100%)	42 (46.1%)
40–59	5 (12.5%)	9 (45%)	0	4 (40%)	6 (54%)	0	0	24 (26.4%)
60–up	4 (10.0%)	5 (25%)	2 (28%)	1 (10%)	2 (18%)	0	0	14 (15.4%)
Total	39 (100%)	19 (100%)	7 (100%)	10 (100%)	11 (100%)	3 (100%)	2 (100%)	91 (100%)

Summary. The records of 96 cases of acute pericarditis diagnosed in a general hospital over a 16-year period were reviewed with special regard to the causative agents involved. A classification similar to the one proposed by Harrison and Resnik was used and it was noted that rheumatic fever accounted for 40.6%, purulent pericarditis 19.8%, tuberculous pericarditis 7.3%, benign non-specific pericarditis 10.4%, uremia 11.5%, neoplasm 3.1%, and the so-called collagen diseases 2.1% of the 96 cases. There remained 5.2% of the total which could not be attributed to any cause. The clinical features are compared in the different forms of acute pericarditis.

REFERENCES

1. **Ada, A. E., Jones, O. R., and Sheeran, A. D.:** J. Thor. Surg., **20,** 28, 1950.
2. **Barnes, A. R., and Burchell, H. B.:** Am. Heart J., **23,** 247, 1942.
3. **Bellet, S., and McMillan, T. M.:** Arch. Int. Med., **61,** 381, 1938.
4. **Bing, H. I.:** Acta. med. scand., **80,** 29, 1933.
5. **Bisgard, J. D.:** Am. J. Surg., **17,** 1, 1932.

6. **Bourne, W. A.:** Brit. Med. J., **2,** 579, 1949.
7. **Brown, M. G.:** New Eng. J. Med., **244,** 666, 1951.
8. **Burchell, H. B.:** Modern Concepts Cardiovascular Disease, **16,** 1947.
9. **Camp, P. D.,** and **White, P. D.:** Am. J. Med. Sci., **184,** 782, 1932.
10. **Camp, P. D.,** and **Clarke, O.:** Virginia Med. Monthly, **77,** 581, 1950.
11. **Carmichael, D. B., Sprague, H. B., Hyman, S. M.,** and **Bland, E. F.:** Circulation, **3,** 321, 1950.
12. **Evans, E.:** J. Am. Med. Assn., **143,** 954, 1950.
13. **Feder, I. A., Hoffman, J.,** and **Sugar, H.:** Am. J. Med. Sci., **220,** 144, 1950.
14. **Finklestein, D.,** and **Klainer, M. J.:** Am. Heart J., **28,** 385, 1944.
15. **Finney, J. O.,** and **Morgan, J. O.:** J. Med. Assn. Alabama, **9,** 81, 1939.
16. **Friedberg, C. K.:** Diseases of the Heart. Philadelphia, W. B. Saunders Co., 1949, pp. 563, 588.
17. **Fuller, C. C.,** and **Quinlan, J. W.:** New Eng. J. Med., **299,** 399, 1943.
18. **Gilley, E. W., McCord, M. D.,** and **Taguchi, J. T.:** Am. J. Med. Sci., **222,** 249, 1951.
19. **Graybiel, A., McFarland, R. A., Gates, D. C.,** and **Webster, F. A.:** Am. Heart J., **27,** 524, 1944.
20. **Harrell, G. T.,** and **Johnston, C.:** Am. Heart J., **25,** 505, 1943.
21. **Harrison, T. R.,** and **Resnick, W. H.:** Principles of Internal Medicine. Philadelphia, Blakiston Co., 1950, p. 1305.
22. **Levy, R. L.,** and **Patterson, M. C.:** Am. J. Med., **8,** 34, 1950.
23. **Logue, R. H.,** and **Wendkos, M. H.:** Am. Heart J., **36,** 587, 1948.
24. **Martin, W. J.,** and **Dardinski, V. J.:** Arch. Ped., **61,** 458, 1944.
25. **McCord, M. D.,** and **Taguchi, J. T.:** Arch. Int. Med., **87,** 727, 1951.
26. **McFarland, J.:** J. Am. Med. Assn., **37,** 1507, 1901.
27. **Nathan, D. A.,** and **Dathe, R. A.:** Am. Heart J., **31,** 115, 1946.
28. **Noth, P. H.,** and **Barnes, A. R.:** Arch. Int. Med., **65,** 291, 1940.
29. **Noy, R. M.,** and **Boyer, N. H.:** Am. Heart J., **32,** 222, 1946.
30. **Pohl, A. W.:** Ann. Int. Med., **32,** 935, 1950.
31. **Porter, W. B., Clarke, O.,** and **Porter, R. R.:** J. Am. Med. Assn., **144,** 749, 1950.
32. **Preble, R. B.:** J. Am. Med. Assn., **37,** 1510, 1901.
33. **Pyrah, L. N.,** and **Paine, A. B.:** Lancet, **1,** 905, 1933.
34. **Sease, R. H.,** and **Beckwith, J. R.:** Virginia Med. Monthly, **76,** 629, 1949.
35. **Smalley, R. E.,** and **Ruddock, J. C.:** Ann. Int. Med. **25,** 799, 1946.
36. **Smith, H. L.,** and **Willius, F. A.:** Arch. Int. Med., **50,** 410, 1932.
37. **Stepman, T. R.,** and **Owyang, E.:** Ann. Int. Med., **27,** 914, 1947.
38. **Stone, W. J.:** J. Am. Med. Assn., **73,** 254, 1919.
39. **Taubenhaus, M. M.,** and **Brams, W. A.:** J. Am. Med. Assn., **142,** 973, 1950.
40. **Urschel, D. L., Bondy, P. K.,** and **Salley, S. M.:** New Eng. J. Med., **233,** 399, 1945.
41. **Vander Veer, J. B.,** and **Norris, R. F.:** Am. Heart J., **14,** 31, 1937.
42. **Vander Veer, J. B.,** and **Wagner, J. A.:** Clinics, **5,** 96, 1946.
43. **White, P. D.:** Heart Disease, New York, Macmillan Co., 3rd ed. 1944, p. 641.
44. **White, P. D.:** Ann. West. Med. & Surg., **2,** 64, 1948.

"MERCURIAL-FASTNESS" IN PATIENTS WITH CONGESTIVE HEART FAILURE: CORRECTION OF THIS STATE BY THE ADDITION OF PYRIDOXINE

By Samuel Waldman, M.D.
AND
Louis Pelner, M.D.
BROOKLYN, NEW YORK

The discovery of mercurial diuretics was one of the signal advances in the management of congestive heart failure. Together with digitalization, this medication remains the sheet anchor in the treatment of this common ailment. Treatment with the mercurials, when adequate digitalization alone has become unsatisfactory, has added years of relatively comfortable existence to the lives of untold thousands with heart failure. Because of this prolongation of life and the repetitious treatment required with these diuretics, a relative "fastness" occurs rather commonly. Throughout the years, several medications have been added to augment the effects of the mercurials, to prolong their action and to break the state of "fastness."

Some of the methods used for augmentation of the mercurials are: Adequate digitalization, acidification with ammonium chloride or nitrate[8], changing the type of mercurials, rest periods between injections and the use of combinations of mercurials with other substances. Some of the combinations that have proven successful for various periods of time are mercurials given with sodium dehydrocholate[21], with ascorbic acid[18] and with aminophyllin[20].

One or another of these extenders is usually successful. The purpose of this paper is to document trials with a substance that has proven to be satisfactory when other aids have failed. In all the cases of "mercurial-fastness" that we have encountered so far, pyridoxine (100 mg.) when added to the mercurial has resulted in satisfactory diuresis.

Method of Therapy. In the patient responding well to the mercurial being used, it should obviously be continued, since no remarkable increase in diuresis can be expected from the Mercuhydrin-pyridoxine combination in such an instance. Actual measurement of urinary output, however, has convinced us that the addition of pyridoxine to the mercurial augments the urinary output by about 60%. This. in itself, is not remarkable since ascorbic acid will itself augment the diuresis attributable to mercury by 50%.

It may be possible to prevent "mercurial-fastness" by changing the mercurial occasionally, even if the one being used is performing satisfactorily. Thus, mersalyl with theophylline or Mercuzanthin or mercaptomerin may be alternated with Mercuhydrin. However, it is our experience that changing the mercurial has no effect when the patient has become "mercurial-fast."

In the "mercurial-fast" patient, pyridoxine, 100 mg., is added to 2 cc. of the mercurial, and the mixture is injected intramuscularly or intravenously. The only mercurial that we have used in this mixture so far has been Mercuhydrin.

We do not have enough cases to compare statistics on each mercurial or each combination, but we feel the results in each individual patient is perhaps even more significant. When a patient in severe cardiac decompensation becomes "mercurial-fast," and this new combination produces a diuretic response, the result is so dramatic that a chance effect is extremely unlikely, other things being equal.

It has been stated that if the mercurial is withheld for a week or two in a resistant patient, the drug will thereafter work. This may be so, but the severely ill patient with edema, ascites, hydrothorax and edematous involvement of the skin can hardly be offered a waiting period safely, until tolerance is regained.

Salt depletion in patients on a low salt diet and on frequent mercurial injections is a real danger, and may result in uremia and death[11]. We constantly guard against this eventuality by employing a modification[2*] of the simple Fantus test[3] for chlorides in the urine.

In all of our patients, the modified Fantus* than 1016, less than three grams of sodium chloride per liter suggests depletion[12]. If the urine contains 4 gms. per liter or more, the patient is unlikely to be suffering from salt depletion.

In all of our patients, the modified Fantus test is done routinely, and if salt depletion threatens, sodium chloride is immediately added to the diet. In spite of this fact, "mercurial fastness" may develop. Other methods have to be found to remedy this resistance.

Ten patients with "mercurial-fastness" have been treated so far with the "Mercuhydrin-pyridoxine combination with salutary effects. To avoid repetition only 5 of these are detailed below. Case 1 is a patient treated with large doses of mercurial drugs in the face of "mercurial-fastness" with disastrous results[1,4,5,9]. The results in this case stimulated us to seek other means of overcoming mercurial refractoriness.

CASE 1: R.B., male, aged 65, was first treated by one of us in December, 1949. Complicating an episode of primary atypical pneumonia, he developed a phlebothrombosis and suffered a pulmonary embolus. A short time after this, he developed shortness of breath on slight exertion, nocturnal dyspnea and slight edema of both ankles. He was digitalized rapidly with digitoxin, given a maintenance dose of 0.1 mg. per day, and was started on Mercuhydrin, at first once a week, and later twice a week, with satisfactory improvement. He never had any symptoms suggestive of either coronary thrombosis or congestive heart failure prior to the initial episode of pneumonia.

The past history revealed a mild diabetes of 25 years' duration, complicated by retinitis. Two brothers died of coronary occlusion and a third of a cerebral vascular accident.

Physical examination revealed a short, stocky, obese, chronically ill male adult, somewhat dyspneic and orthopneic. He had normal sinus rhythm with occasional premature contractions. The heart sounds were distant, of poor quality and the pulmonary second sound was louder than the aortic sound. There was a faint systolic murmur at the apex. Crepitant rales were present at both bases. The liver was enlarged to 4 finger-breadths below the costal margin. Very slight ankle edema was present.

Roentgenograms revealed cardiac enlargement with pulmonary congestion, the vessels of the pelvis and both lower extremities showed arteriosclerotic changes. An electrocardiogram showed left axis deviation and normal sinus rhythm. The laboratory data were essentially negative.

The patient did well on a maintenance dose of 0.1 mg. of digitoxin daily and Mercuhydrin 2 cc. with vitamin C, 100 mg. intramuscularly once weekly. He subsequently required 2 injections per week. The weight ranged from 165 to 169 pounds. A urine chloride test done on the date of each mercurial injection revealed an adequate output, and therefore presumably an adequate serum sodium level.

The patient discontinued mercurial therapy and was treated with exchange resins elsewhere, under which he did poorly. His weight increased 10 pounds to 179 pounds. Administration of Mercuhydrin, 2 cc. with vitamin C, 100 mg., every other day resulted in a poor diuretic response.

The urinary chloride test revealed a low chloride content so that the salt intake was increased. The patient continued to gain weight. Lipo-adrenal cortex hormone was given in addition to the mercurial and vitaman C. Urinary output continued to be poor.

A cardiologist consultant advised that the patient be given 2 cc. of Mercuhydrin every 12 hours and have one glass of water followed by one glass of Lonalac (salt-free

* 10 drops of urine are measured in a test tube, and one drop of potassium dichromate solution (20%), the indicator, is added. Using a separate dropper, an 0.73% solution of silver nitrate is added drop by drop until the color changes sharply from yellow to brown, and the brown color remains after agitation. The number of drops needed to produce the end-point divided by 4 is equal to the number of grams of sodium chloride per liter of urine. Each drop is equal to 250 mg. of chloride per liter of urine, expressed as sodium chloride or 100 mg. of sodium per liter. The silver nitrate reagent is made by dissolving .146 gm. of silver nitrate in 20 cc. of water.

milk), alternating at intervals of one hour a day making 12 glasses in all. This regime was kept up for one week, yet his weight increased to 194 pounds.

He was thereupon taken to the hospital of the consultant, where the dose of Mercuhydrin was increased to 2.5 cc. twice daily and after 2 days was increased to 3.5 cc. twice daily. His weight did not increase significantly, but it did not decline and the urinary output was very poor. The Mercuhydrin was given at this rate for a period of 7 days, until one day the patient was found dead in bed. An autopsy was not done so that the exact cause of death could not be ascertained.

COMMENT. This patient is described at length, in order to highlight the possible danger of large doses of the mercurials in a "mercurial-fast" patient. This patient did well on Mercuhydrin with vitamin C injections for some time. Then he was given ion exchange resins for about 3 weeks; finally he became resistant to Mercuhydrin with vitamin C. Inclusion of sodium chloride in the diet because of a mild salt depletion and the addition of Lipo-Adrenal Cortex extract did not improve the situation. Finally repeated twice-daily injections of large doses of Mercuhydrin were given even in the absence of a diuretic response.

CASE 2: Mrs. M. L., aged 60, was first seen in acute cardiac failure. Her diagnosis was aortic insufficiency, enlarged heart on a luetic basis. She had had attacks of severe precordial pain which sometimes lasted for one or two hours, but which subsided with the sublingual administration of nitroglycerin. These attacks were presumed to be due to luetic ostial sclerosis. Her blood pressure was 210/80. Her initial weight, when first seen, was 210 pounds. She was digitalized and was given Mercuhydrin, 2 cc., intramuscularly once weekly. In addition, she was given ammonium chloride 3 grams daily. Because of a weight gain to 212 pounds, 2 cc. of Mercuhydrin was combined with 100 mg. vitamin C and this was given twice weekly. The weight increased in spite of this treatment until a weight of 238 pounds was reached. At that time, in addition to the marked edema of the legs, both of her breasts were markedly edematous. Instead of ascorbic acid, pyridoxine (100 mg.) was substituted, with a weight loss of about 2 pounds per visit. These medications were continued twice a week for the following 6 months. At this time her weight was about 185 pounds. Mercuhydrin was given again with vitamin C, following which a satisfactory diuresis was obtained.

COMMENT. The combination of Mercuhydrin with pyridoxine seemed to affect favorably the "mercurial fastness' of this patient, after Mercuhydrin with ascorbic acid proved ineffectual. Later, this latter combination was continued with satisfactory results.

CASE 3: Mr. A.B., aged 51, was treated in 1948 and again one year later for acute myocardial infarction. On March 15, 1950, he was seen with acute left heart failure. He was digitalized and given Mercuhydrin 2 cc. with ascorbic acid, 100 mg., once a week. Under this regimen his weight dropped and remained around 172 pounds until the end of 1950. In May, 1951 he required 2 injections per week of this combination. His weight ranged around 160 pounds until October 17, 1951. At that time, in spite of 2 injections per week, he gained 8 pounds, and the edema became so massive that another method was sought to improve his condition. Previous to this time, the chloride output ranged between 3 and 4 gm. per liter, but on October 19, 1951, at the time of the greatest weight gain, the chloride output was 1 gm. per liter. He was placed on added salt, approximately 5 gm. per day, divided throughout the day. In addition to the combination previously given, 2 cc. of Lipo-Adrenal Cortex was added to the therapy. The weight on October 24 had increased 4½ pounds. At that time the urine showed 4 gm. of chloride per liter which was within the normal range. However, the edema became more and more massive, and the urinary output on the day of Mercuhydrin therapy was only 1200 cc. The addition of 2 cc. of Lipo-Adrenal Cortex extract every other day failed to improve his condition.

Despite this therapy general anasarca developed. The chloride output continued at 3 to 4 gm. per liter. His weight mounted to 191 pounds. It was then decided to try, somewhat as a last resort. the combination of 2 cc. Mercuhydrin, plus 100 mg. pyridoxine. That day he had a diuresis of 6,000 cc. and lost 6 pounds in weight. He was given this last combination 3 times a week. Satisfactory diuresis followed injection so

that his weight fell to 150 pounds. He has very slight edema of both ankles; the chest, abdomen and skin are free of fluid, except for the slight amount previously mentioned. Following 3 of these injections, the urine test showed 1 to 1½ grams chloride excretion per liter, and in spite of this there was profuse diuresis with the new mixture.

COMMENT. This patient was at first responsive to Mercuhydrin with added vitamin C injections. He then became "mercurial fast." Therapy to correct a moderate salt depletion was ineffective in overcoming the resistance. Lipo-Adrenal Cortex extract was ineffectual, producing a slight increase in diuresis, but a weight gain at the same time. Combining Mercuhydrin with pyridoxine broke the "fastness" of this patient.

CASE 4: J.K., male aged 67, was first treated in 1944 for severe recurrent attacks of coronary thrombosis. He did well for several years, but since 1950 he developed increasing shortness of breath and edema of the legs. At that time he weighed 214 pounds. With a weekly injection of Mercuhydrin, 2 cc., and with vitamin C, 100 mg., the edema subsided satisfactorily and the dyspnea improved. He would intermittently discontinue therapy with the result that edema and dyspnea recurred and finally ascites also became manifest. However, on several occasions a satisfactory diuresis occurred with Mercuhydrin 2 cc. and vitamin C, 100 mg. once weekly.

On September 15, 1951, he was seen again after a prolonged break in therapy. Generalized anasarca was present. Mercuhydrin with vitamin C, in the dosage previously stated, was given daily for 6 days without any beneficial effect whatsoever, and with an increase of 5 pounds in weight. The urine contained between 4 and 5 gm. of chloride per liter. The patient was growing progressively worse and there was likelihood of impending death. Mercuhydrin 2 cc. with 0.5 gram aminophyllin was given intravenously on 2 successive days. There was a poor diuretic response and a gain in weight of 2 pounds.

The following day, 2 cc. of Mercuhydrin was combined with 100 mg. pyridoxine. On this day there was a profuse diuresis equalling approximately 3500 cc. In 72 hours the dosage was repeated, and there was marked diminution of the edema of the scrotum, and penis and thighs. He was given 2 more injections at this rate. His condition improved to such an extent that only one injection of Mercuhydrin, plus pyridoxine was necessary at weekly intervals. He is now responding satisfactorily to this combination.

COMMENT. This patient improved initially with injections of Mercuhydrin with added ascorbic acid. After one of his frequent breaks in the course of therapy, he ceased to respond to this combination. Addition of 0.5 gram of aminophyllin to each 2 cc. of Mercuhydrin did not restore a response in this patient. Combination of pyridoxine with Mercuhydrin proved successful.

CASE 5: T.K., a 56-year old white male, was under treatment for 4 years for chronic cor pulmonale. This condition followed chronic bronchial asthma with resultant pulmonary fibrosis. He was in a state of chronic cardiac failure.

On a regime of digitoxin, 0.3 mg. daily, ammonium chloride 3 to 6 gm. daily, low salt diet, Mercuhydrin 2 cc., twice weekly, as well as repeated phlebotomies and antiasthmatic therapy, the patient had been kept fairly comfortable. The mercurial was administered intravenously to this patient because it resulted in better diuresis than when given intramuscularly.

When the patient began to fail in his response to mercurials, the following augmentation procedures were used sequentially: Addition of aminophyllin, ascorbic acid, Lipo-Adrenal Cortex extract, and Decholin, along with mercurial. Diuretic action was enhanced in a fluctuating manner and was inconstant. The addition of pyridoxine hydrochloride, 100 mg. to the mercurial caused a drop in weight of 6 pounds in the first 24 hours. Clinical improvement accompanied the diuresis which persisted on the combined therapy. However, because of the real chronicity of the condition, the patient is still in a state of chronic congestive heart failure three months after initiation of this therapy. He is more comfortable than he had been in over a year and returned to work as a presser. Combination injections are still being used since the administration of the mercurial alone caused an unsatisfactory output of urine.

COMMENT. Mercurial resistance and mercurial combination resistance was

overcome in a chronic cor pulmonale patient in chronic congestive heart failure by combining pyridoxine with the mercurial.

CASE 6: M.C., female, aged 68 years, has been under the care of one of the authors since 1938 for chronic rheumatic heart disease. mitral stenosis and insufficiency and aortic stenosis and insufficiency with chronic congestive failure. Auricular fibrillation occurred first in paroxysmal attacks and then became permanent. In order to maintain a fair state of compensation, the patient had been on constant digitalization, diuretic salts and mercurials. The low salt regime was instituted when this became the vogue. Despite all these forms of treatment, there is constant dyspnea to some extent, and lower limb edema.

For the past 6 years the patient was being maintained at a weight of 140 pounds and was receiving Mercuhydrin plus ascorbic acid intravenously. This method of administration was most effective. When the mercurial was discontinued, the patient would develop dyspnea and edema of the lower extremities. In November, 1950, despite a similar continued therapy with added cation exchange resins, the patient noted a decrease in urinary output, increasing dyspnea both on exertion and at rest and increasing peripheral edema. Her weight was 147 pounds. The patient was then given mercurial plus pyridoxine every other day. A loss of 5 pounds followed the first injection, 3 pounds after the second. Following a stationary period a loss again of 4 pounds followed so that a weight of 135 pounds was attained. This patient then failed to respond further to the combined mercurial and pyridoxine intravenously. Other combinations were then utilized and a return to successful diuresis was obtained by altering the various combinations.

COMMENT. Mercurial resistance developed in a chronic rheumatic cardiac in chronic congestive failure despite all attempts to break it, including low salt routine and cation exchange resins. With combined Mercuhydrin and pyridoxine therapy the patient was again restored to the previous state of diminished compensation. Refractoriness developed to this combination and it became necessary to resort to previous mixtures in order to again obtain diuresis.

Discussion. The method of action of pyridoxine in overcoming "mercurial-fastness" is not known, since there is no mention of diuretic action in any of the available literature on pyridoxine. We, therefore, feel that whatever action this substance has must be on an enzymatic level of activity. Studies to prove or disprove this contention have already been projected.

Recent studies[6,14] of the action of the mercurials at the enzymatic level, indicate a correlation between the diuretic action of the mercurial compounds and the inhibition of the succinic-dehydrogenase enzyme system of the kidney. When this system is blocked by the presence of mercury, there is a marked interference with the tubular reabsorption of sodium and water. Thus these 2 excretory products are present in increased amounts in the urine. The activity of the succinic-dehydrogenase enzyme system depends on its SH groups, and mercury blocks the activity of this group. Introduction of additional SH groups, as by giving BAL after the mercurial, immediately restores normal function of the cells of the renal tubules and the loss of sodium and water is stopped. How pyridoxine fits into this enzymatic picture remains to be shown.

There is some evidence to show that the urine of patients with cardiac failure contains an antidiuretic substance[13]. This presumably is similar or identical in activity with the pituitary antidiuretic hormone. The physiological antagonists to the pituitary antidiuretic hormones are the adrenocortical hormones. The adrenocortical hormones prevent the increased tubular reabsorption of water (caused by in-

creased pituitary anti-diuretic hormone). Thus their locus of action is the same as that of the mercurials. Indeed, Lloyd and Lobotsky[10] stated that in severe cardiac failure with edema, large doses of adrenal cortex hormones (Lipo-Adrenal Cortex (Upjohn)) caused a marked diuresis. We were unable to entirely confirm this observation in cases of heart failure with resistance to the mercurials, since these are the patients in whom one would look for help from the hormones. Although there was a slight increase in urinary output, there was also an increase in weight, indicating both an increased urinary output, and also an increased retention. This is a known effect of the adrenocortical hormones. Since the amounts of hormone used by Lloyd and Lobotsky are not indicated in their published article, exact comparison is impossible. However, we have documented elsewhere evidence to show a salutary effect in cases of cirrhosis of the liver with marked ascites and edema[15].

While we have obtained benefit in some patients with each of the combinations discussed, the patients presented in this paper are those who did not respond to other combinations, but did respond to the Mercuhydrin-pyridoxine mixture. This is not to say that the other combinations do not have definite value, but that the clinician should have another combination available when the others have proven fruitless.

The low salt syndrome is an established danger in the treatment of patients with mercurial diuretics[7,11,16]. We constantly guard against this eventuality by using a modification of the Fantus test for the determination of chloride in the urine. Besides the low salt syndrome, a chloride depletion syndrome has recently been described by Schwartz[17] and Stock[19]. They claim that some patients lose large amounts of chloride, rather than sodium chloride, during diuresis. In the instances described by Schwartz, the patients developed hypochloremia and alkalosis. These patients became unresponsive to mercurials. Administration of ammonium chloride corrected the electrolyte imbalance, after which the mercurial again produced a diuresis. Most of our patients have had a trial with ammonium chloride; while ammonium chloride enhances the diuresis in a responsive patient, it usually fails to affect the patient who is "mercurial-fast."

Summary. 1. Ten patients with severe congestive heart failure and "mercurial-fastness" were treated satisfactorily with a Mercuhydrin-pyridoxine mixture.

2. The danger of treatment with large doses of mercurials in the absence of a diuretic response is stressed.

3. The mode of action of pyridoxine in breaking "mercurial-fastness" is unknown, but it is probably effective at an enzymatic level.

4. Mercurial resistance may become manifest in any combination mixture and requires changing from one to another to maintain successful diuresis.

REFERENCES

1. **Bruno, M. S.:** New Eng. J. Med., **239**, 769, 1948.
2. **Bryant, J. M., Iob, V., Phillips, G. L.,** and **Blecka, E. E.:** J. Am. Med. Assn., **140**, 670, 1949.
3. **Fantus, B.:** J. Am. Med. Assn., **107**, 14, 1936.
4. **Gold, H.:** J. Am. Med. Assn., **132**, 547, 1946.

5. **Grossman, J., Weston, R. E., Lehman, R. A., Halperin, J. P., Ullmann, T. D., and Leiter, L.:** J. Clin. Invest., **30,** 1208, 1951.
6. **Handley, C. A., and Lavik, P. J.:** J. Pharmacol. & Exper. Therap., **100,** 115, 1950.
7. **Jaffe H. L., Master, A. M., and Dorrance, W.:** Am. J. Med. Sci., **220,** 60, 1950.
8. **Keith, N. M., and Whelan, M.:** J. Clin. Invest., **3,** 149, 1926.
9. **Kwit, N. T., Modell, W., Hanlon, L. W., Benton, J. G., Cotlove, E. W., Pearlmutter, M., Greenberg, S. M., Kramer, M. L., and Gold, H.:** Fed. Proc., **7,** 236, 1948.
10. **Lloyd, C. W., and Lobotsky, J.:** J. Clin. Endocrinology, **10,** 318, 1950.
11. **MacGuire, W. B.:** J. Am. Med. Assn., **137,** 1377, 1948.
12. **Marriott, H. L.:** Water and Salt Depletion. Springfield, C. C Thomas, 1950.
13. **Mercu, B. A., Rokaw, S. N., and Massie, E.:** Circulation, **2,** 409, 1950.
14. **Orth, O. J.:** Wisconsin Med. J., **49,** 1133, 1950.
15. **Pelner, L., and Waldman, S.:** In press.
16. **Schroeder, H. A.:** J. Am. Med. Assn., **141,** 117, 1949.
17. **Schwartz, W. B.:** Bull. New Eng. Med. Center, **12,** 213, 1950.
18. **Shaffer, C. F.:** J. Am. Med. Assn., **124,** 700, 1944.
19. **Stock, R. J., Mudge, G. H., and Nurnberg, M. J.:** Circulation, **4,** 54, 1951.
20. **Vogl, A., and Esserman, P.:** J. Am. Med. Assn., **147,** 625, 1951.
21. **Weigand, F. A.:** J. Am. Med. Assn, **105,** 2034, 1935.

MILD HEMOPHILIA: AN ALLELIC FORM OF THE DISEASE*

By JOHN B. GRAHAM, M.D.**
ASSISTANT PROFESSOR OF PATHOLOGY

WILLIAM W. MCLENDON, A.B.
STUDENT ASSISTANT IN PATHOLOGY

AND

K. M. BRINKHOUS, M.D.
PROFESSOR OF PATHOLOGY

(From the Department of Pathology, University of North Carolina, Chapel Hill, N. C.)

CLASSICAL hemophilia is an hereditary disease of blood coagulation transmitted as a sex-linked recessive characteristic. Those affected have frequent hemorrhages with some degree of joint disability, and occasionally die from massive bleeding. It has been recognized that the severity of the disease varies considerably from patient to patient. There has also been an impression that the severity is relatively constant within a family. Recently, reports of mild forms of the disease with almost inapparent clotting defects have appeared. Merskey[16,17] noted that 9 of 51 hemophiliacs had normal clotting times and that 5 had normal or nearly normal prothrombin consumption indices. Dunn and Lyons[7] found hemophilic siblings and cousins with diseases of strikingly different degrees of severity. The severity of the symptoms, particularly the occurrence of hemarthrosis, was proportional to the alteration in the clotting mechanism. In each series of cases both mild and severe hemophilia appear to have been present in individual families.

Recently we have studied a family with a hemorrhagic diathesis, apparently a form of hemophilia, which is uniformly mild in its manifestations. The disease had not been diagnosed previously, although there were 79 living members of the family, including 14 affected males. In our studies the level of antihemophilic factor (AHF), the plasma factor lacking in hemophilia[1], was determined by two different assay procedures[9,14]. These assays, developed in this laboratory, have made it possible to separate the affected males and some of the heterozygous females from the other members of the family, when all other clotting tests were normal or equivocal. Our data indicate that this mild hemorrhagic disease, like classical hemophilia, is inherited as a sex-linked recessive characteristic.

Course of the Malady. The disease is, by all criteria, the mildest form of hemophilia which we have observed. No member of the family has ever had hemarthrosis, nor has anyone died of hemorrhage. The affected males complain of easy bruising, difficulty in stopping the bleeding from razor cuts, and prolonged bleeding after tonsillectomy or tooth extraction. The older men have lived active lives, as textile workers chiefly, and appear to suffer only from the diseases of middle age unrelated to hemophilia. They are said by their physicians to be "free bleeders" but not dangerous bleeders. Bleeding usually

*This investigation was supported in part by a research grant from the Division of Research Grants and Fellowships of the National Institutes of Health, U. S. Public Health Service.
**Markle Scholar in Medical Science.

develops in association with obvious trauma, accidental or surgical. They appear not to have hemorrhagic crises.

A clear history of hemorrhagic tendency in the women of the family is lacking. Easy bruising, especially about the thighs, and menorrhagia are the commonest complaints both in the apparently normal women as well as in those who are heterozygous. Abstracts of the histories of two affected males typical of the group are recorded below.

PROPOSITUS: III, 34 (Fig. 1.) This 18-year old male college student has always bruised easily. At 5 years, tonsillectomy was followed by bleeding for 11 days, requiring 4 transfusions. At 6 years, two teeth were knocked out. The sockets bled freely for several days, necessitating a transfusion. At 9 years, bleeding followed tooth extraction and required one transfusion. He has never had joint trouble and plays basketball frequently without any difficulty.

MATERNAL UNCLE OF PROPOSITUS: II, 5 (Fig. 1). This 50-year old male says that he is in excellent health. He has always bruised easily, and occasional nosebleeds have been difficult to stanch. Tooth extractions have invariably been attended by prolonged bleeding, lasting 2 to 4 days, but not enough to require transfusion. Tonsillectomy, at 34 years, caused pharyngeal bleeding which lasted 2 weeks. He developed a peptic ulcer at age 42 which bled for several weeks and required 7 transfusions. There has never been joint swelling, pain or limitation of motion.

Materials and Methods. BLOOD for the testing of our subjects was obtained from a vein in the antecubital fossa using silicone-treated syringes (General Electric Dri-Film 9977). Venipuncture was made with a separate syringe and the first several cc. of blood obtained was discarded. When plasma was required, 9 volumes of blood were mixed with one volume of 0.1 M sodium oxalate and the cells sedimented at 4000 *g* for 10 to 15 minutes in siliconed tubes.

CLOTTING TIMES were performed at 28°C. in 8 x 75 mm. serological test tubes, both plain and silicone-treated, by a modified Lee and White method[15].

PLATELETS were counted by a modification of Nygaard's method[20].

BLEEDING TIMES were determined by the technique of Ivy, Shapiro and Melnick[12] using a spring-driven lancet set to cut to a depth of 2 mm.

PROTHROMBIN was determined by the two-stage method[23], modified by the addition of Factor V[21] to the diluting fluid.

PROTHROMBIN TIME was determined by the method of Quick[22].

PROTHROMBIN UTILIZATION tests were done by two procedures. Both the one-stage method[13] and the two-stage method of Buckwalter, Blythe and Brinkhous[4] were used. With the latter method, the time required for conversion of 50% of the prothrombin in the clotting blood was determined by interpolation from a graph in which per cent prothrombin was plotted against time after collection of the blood. This time value has been designated as the *prothrombin half-life*, and is expressed in minutes. It is inversely proportional to the rate of prothrombin utilization, and provides a simple and apparently accurate expression of the rate of prothrombin consumption.

PLASMA AHF was determined by the simplified method of Langdell, Wagner and Brinkhous[14], using plasma from a classical hemophiliac as the test medium. The results are expressed in percent of the mean AHF value (100%) of a control group of 28 normal adults of both sexes. The range of this group was 68 to 165% and the standard deviation 28%. Freshly prepared plasma from a single member of the group, whose AHF was 78% of the mean, served as the control for each assay. The plasma AHF levels in those persons of the family with low values by the simplified procedure were determined also by our earlier method[9]. Plasmas were adsorbed with 40 mg. $BaSO_4$ per cc. before testing.

CAPILLARY FRAGILITY was tested by maintaining a blood pressure cuff on the arm at a pressure midway between systolic and diastolic pressure for five minutes.

AC-GLOBULIN was determined by the method of Ware and Seegers[25].

SERUM ACCELERATOR evolution during clotting was observed by the method of Langdell, Graham and Brinkhous[13].

PLASMA ANTITHROMBIN studies and investigation of *circulating anticoagulants* were made by the methods of Dreskin and Rosenthal[6].

COLOR VISION was tested with the Ishihara color charts.

Results. LABORATORY FINDINGS. The results of the laboratory tests performed on a group of normal controls, a group of heterozygous females, and a group of bleeder males are shown in Table 1. An examination of the results of Tests 1 to 6 of the Table demonstrates the mild character of the clotting abnormality in this family. It was difficult, if not impossible, to single out an affected individual on the basis of clotting time, platelet count, bleeding time or prothrombin utilization values. Yet there can be little doubt that the difference between the mean clotting times of the controls and the affected men is significant. A similar statement can be made about prothrombin consumption. On the other hand, the AHF assay differentiates the affected males from the controls in an individual case without difficulty (Test No. 7, Table 1). With a single exception, the affected males have lower levels than the heterozygous females also. This exception, III, 33 (Fig. 1) is the brother of two affected males. He has an AHF level of 45% but no symptoms. He may well be carrying the hemophilia gene; if so, it has a milder effect in him than in his male relatives. It should be noted that the results of Test No. 8, obtained

TABLE 1.—COMPARATIVE CLOTTING DATA ON NORMAL CONTROLS HETEROZYGOUS FEMALES AND BLEEDER MALES

Test No.	*Test*		*10 Normal Controls*	*10 Heterozygous Females*		*6 Affected Males*
				4 Type "A"	*6 Type "B"*	
1	Clotting Time, glass (minutes)	mean	8.9	9.8	10.6	13.3
		σ	.9	.9	1.6	1.3
		minimum	7.5	9.0	8.5	12.0
		maximum	10.0	11.0	12.0	15.0
2	Clotting Time, Silicone (minutes)	mean	11.5	15.1	14.8	18.6
		σ	3.2	2.2	3.6	3.9
		minimum	9.0	12.0	11.5	14.5
		maximum	17.5	17.0	21.0	24.5
3	Platelets per mm. (thousands)	mean	256.0	—	237.0	244.6
		σ	62.0	—	63.0	88.0
		minimum	169.0	—	175.0	128.0
		maximum	330.0	—	335.0	334.0
4	Bleeding Time, (minutes)	mean	4.4	4.9	5.3	5.8
		σ	1.8	1.8	1.9	1.2
		minimum	2.0	3.0	4.0	4.5
		maximum	6.0	7.0	8.5	7.5
5	Modified One-Stage Prothrombin Time, (seconds)	mean	47.0	—	26.0	26.0
		σ	11.0	—	7.0	18.0
		minimum	31.0	—	17.0	16.0
		maximum	70.0	—	32.0	62.0
6	Prothrombin Half-life, (minutes)	mean	36.0	—	41.0	45.0
		σ	3.0	—	7.0	4.0
		minimum	31.0	—	34.0	38.0
		maximum	41.0	—	49.0	50.0
7	Plasma AHF, Simplified method, (% normal control)	mean	96.0	70.0	42.0	19.0
		σ	31.0	14.0	7.0	5.0
		minimum	68.0	60.0	31.0	9.0
		maximum	149.0	88.0	54.0	25.0
8	Plasma AHF Original Method, (% normal control)	mean	—	—	46.0	17.0
		σ	—	—	8.0	3.0
		minimum	—	—	39.0	12.0
		maximum	—	—	58.0	22.0

with our earlier assay procedure[9], correlate very well with the AHF values obtained with the simplified method.

The data on heterozygous females are of interest. They do not differ significantly either from the controls or the affected males except in regard to AHF levels. Further it will be noted (Test No. 7) that these women fall into two categories: those transmitters with AHF levels in the normal range (Type A) and those with levels intermediate between the normal level and that of affected men (Type B). The significance of this finding will be considered later. Tourniquet tests on all persons shown in Table 1 were negative. There was no deficiency of plasma prothrombin or of fibrinogen. The blood of the propositus contained a normal amount of Ac-Globulin. Serum accelerator evolved during the clotting of his blood

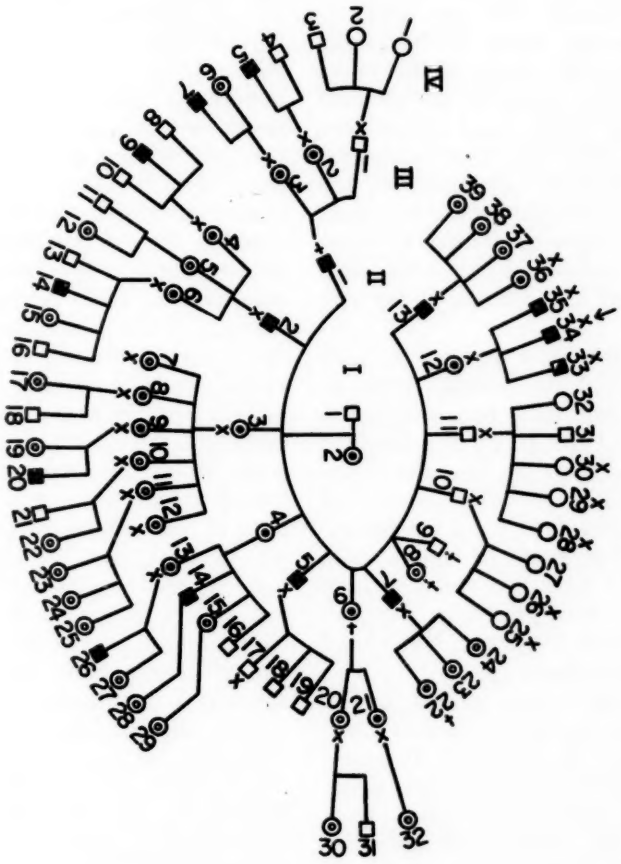


FIG. 1.—Pedigree. Key to symbols: ■ =affected male; ◪ =probably affected male; □ =normal male; ⊙ =heterozygous female; ◎=female of unknown genotype, a potential transmitter; ○ =female of unknown genotype, probably normal for genetic reasons; X =personally tested; † =dead; ‡ =died in infancy. The type A heterozygotes with affected sons are II 3, III 2, III 6 and III9. The Type B heterozygotes with affected sons are II 12, III 3, III 4 and III 13. Type B heterozygotes identified by the AHF assay are III 8, III 21 and III 36.

to the extent that 45 minutes after clotting, the prothrombic activity reached 145% of the control value. This value agrees well with those obtained earlier in similar experiments on normal individuals[13]. Antithrombin was not increased, and no circulating anticoagulant could be demonstrated in the blood of the propositus.

INHERITANCE. The division of male members of the second and third generations of this family into the two phenotypes, normal and affected, is accomplished readily with the AHF assays. The normal males in the family have plasma AHF levels in the range 71 to 112%. The levels of the affected males, on the other hand, have been below 25%, with the single exception noted above. Although none of the males in the fourth generation have been tested, histories similar to those of the older males with low AHF have been accepted as evidence of the disease.

It was found early in working with this family, that the women with affected sons fell into two categories, Type A and Type B, on the basis of AHF levels. Following this discovery, all women with low AHF levels but without affected sons were considered Type B heterozygotes. All women with normal plasma AHF levels and without affected sons were placed in the "unknown" category and are considered potential transmitters.

The pedigree is seen in Fig. 1. The disease appears to be inherited as a sex-linked recessive characteristic. It should be noted that 8 of the 9 living members of the second generation were tested with the battery of tests described above. Twenty-four of the 39 members of the third generation were tested, but none of the fourth generation because of their extreme youth. On examining the family tree, it is noteworthy that in the second generation 5 of 7 brothers were bleeders, while all 4 of the females were transmitters. This preponderance of affected males and heterozygous females does not rule out the hypothesis of a sex-linked recessive mode of inheritance. The male distribution (5:2) is one which might occur one time in 6 by chance, while the female distribution (4:0) is a one in 16 chance occurrence. Taken separately, either distribution has a probability greater than that of the one in 20 chance usually required for rejection of the hypothesis. The Fisher-Wallis test for compounding probabilities from independent tests for significance[24] was applied also, to see whether the hypothesis should be rejected. The result of this test, P=.0578, does not rule out sex-linked recessive transmission. More evidence in favor of the hypothesis is seen in Table 2. It will be noted in the top line that all the classifiable daughters of affected fathers are transmitters, while all of the sons are normal. If we were dealing with an autosomal dominant, this distribution would occur by chance only one time in 512, a highly unlikely probability. In contrast, this distribution is exactly what would be expected for a sex-linked recessive characteristic. Also, none of the children of the normal men are affected, and the children of the heterozygous women in the bottom line fall into 4 classes: normal males, affected males, carrier females, and unknown. These facts also support the sex-linked hypothesis. The other possible mode of inheritance, autosomal recessive, appears to be ruled out by the high frequency of the condition in this family, in spite of the fact that there were no cousin marriages.

Discussion. Clinically the affected males in this family have a mild hemorrhagic disease, which has been present in at least 3 generations. The diagnosis of hemophilia is based on the deficiency of plasma AHF. Support for this diagnosis is furnished by the transmission

of the disease as a sex-linked characteristic, and the absence of changes in other clotting factors which could be responsible for the bleeding diathesis. The disease, however, is quite different from the usual form of hemophilia. Hemarthrosis and fatal hemorrhage are unknown in this family. The clotting defect is so slight that, without the AHF assays, it would have been difficult to be certain that a defect existed at all. Plasma from classical hemophiliacs shows at most only traces of AHF under the conditions of our assays. On the other hand, the bleeder males in this family have as much as 20 to 25% AHF. Not only is this disease milder than that observed in other hemophilic families, but it is milder in its manifestations than hemophilia observed in dogs and swine. Our strain of canine hemophilia is comparable to classical hemophilia in humans[8]. Porcine hemophilia appears to be a less severe form of the disease[3]. Plasma of bleeder swine may contain 10 to 15% as much AHF as normal controls. However, even in this disease, hemorrhagic manifestations are common and fatal hemorrhage frequently occurs.

It is interesting to speculate why members of this family have a hemophilia-like tendency. From other lines of evidence, it appears that the normal clotting system has a five to ten-fold excess of AHF. It has been shown in dogs, *in vitro*, that prothrombin consumption in mixtures of hemophilic blood and normal plasma approximates the normal rate when about 10% of the mixture is normal plasma[8]. Both in man and in dogs, when increasing amounts of normal plasma are added to hemophilic plasma, the cephalin clotting time reaches a minimum when normal plasma is present at about the 15% level[14]. It does not change on addition of larger amounts of normal plasma. These facts seem to indicate that at values of about 20% or higher, clotting and hemostasis are normal, but that with lower values, both may be impaired. It is possible that the affected males in this family have a borderline clotting defect which allows them to sustain slight injury with little or no difficulty, resulting in bruises rather than hematomas, for example. However, in the presence of more extensive injury, as occurs with tonsillectomies or tooth extractions, the available supply of AHF may be seriously depleted, and the demand cannot be met by the fabricating mechanism. It would be interesting indeed to follow the AHF titer in an affected individual under a condition of stress, such as a major operative procedure.

Finding heterozygotes with markedly reduced AHF is surprising in view

TABLE 2.—SUMMARY OF THE PROGENY FROM THE PERSONS OF KNOWN GENOTYPE

Parental Genotypes	*Descendents*					
	Males			*Females*		
	Normal	*Bleeder*	*Unknown*	*Normal*	*Transmitter*	*Unknown*
5 Bleeder Males	4	0	0	0	5	7
3 Normal Males	2	0	0	0	0	9
13 Transmitter Females	8	12	5	0	8	13

of previous studies. Merskey and Macfarlane[19] have tested humans and we[9] have tested dogs heterozygous for hemophilia. Neither study showed any reduction in the plasma antihemophilic activity. We have recently assayed plasmas from 3 mothers and 3 sisters of severe hemophiliacs for AHF. All AHF levels fell in the normal range of 68 to 130%.

The problem of identifying heterozygous and normal women in a group of potential transmitters of classical hemophilia is difficult. If there are affected sons, the heterozygous state is established. However, if there are only normal sons, the normal state is not established. In fact, even if there are 5 normal sons, there are still 3 chances out of a hundred that the mother is heterozygous. With our mild hemophilia, this problem of identification appears to be eased, since roughly half of the heterozygotes have low AHF values. The prediction value of low AHF for heterozygosity should be definitely established by further studies on the 3 women without affected progeny but with low AHF (Fig. 1), as well as on the females of the fourth generation.

The effect of the gene for mild hemophilia appears to be complex. The heterozygotes for classical hemophilia have high AHF levels while possessing a gene, *h*, whose expression in the male is quite severe. Some of the heterozygotes in mild hemophilia have relatively low AHF levels, although they have a gene whose effect in the male is relatively mild. That there is any expression of the gene in the heterozygote raises the question whether the mild hemophilia gene is a dominant one. The fact that some of the heterozygotes have normal AHF levels rules somewhat against this possibility. An attempt was made to study linkage between this gene and the color blindness gene, in order to determine whether the mild hemophilia gene was at the same locus as the classical hemophilia gene. As no color blindness is present in the family, this bit of information is not available. The gene for the mild disease may be either an incomplete recessive or a partial dominant lacking complete penetrance. We are postulating that it is an incomplete recessive carried on the X-chromosome and different from the allele for classical hemophilia. This postulation of an allelomorphic form of hemophilia is not original with us. Haldane[10] made this deduction from Davenport's clinical data[5] earlier. Our laboratory data appear to be accurate and objective enough to lend strong support to the hypothesis. The most likely explanation is that the mild gene is an allelic mutant, occurring at the same locus as the normal (dominant) gene, *H*, and the classical hemophilia gene, *h*. We propose designating the new allele h^m. The small letter *h* is to indicate that the gene is probably recessive to the normal gene, and the superscript *m* is designed to indicate that it is responsible for a mild form of hemophilia.

To determine which hemophilia mutant h^m or *h*, is dominant to the other, it would be necessary to find and study a woman of the genotype $h^m h$. If she were a mild hemophiliac, one might be safe in assuming dominance of h^m. Females of the *hh* genotype in both dogs[2] and humans[11,18] have been found already to have a severe disease identical with the classical hemophilia of males. A mutant h^m, allelic with *h*, suggests that there are other alleles of a series of multiple allelomorphs. Thus, normal alleles to *H* may be common, as *H'*, *H''*, etc., and each may be associated with a characteristic plasma AHF level. This hypothesis would help account for the wide range of AHF levels in our series of normal humans, and the relatively constant level of AHF in a strain of inbred dogs[9].

The mildness of this allelic form of

hemophilia and the difficulty in diagnosis suggest that this disease may have been largely overlooked. It would be of interest to study the numerous unclassified "bleeders" in the population with AHF assay procedures. Many of them may actually be mild hemophiliacs. The simplified AHF assay makes such studies relatively easy, since the test is not difficult to perform and it appears to be more reliable than other simple tests available heretofore.

Summary and Conclusions. A large family with a mild form of hemophilia has been studied. There is no history of hemarthrosis or fatal hemorrhage. The usual clotting tests, including prothrombin consumption tests, are normal or equivocal. Diagnosis depends on the demonstration of definitely reduced antihemophilic activity of plasma (plasma AHF). The disease, like classical hemophilia, seems to be transmitted as a sex-linked recessive characteristic. Some of the heterozygotes show a diminution in plasma AHF. This implies that the gene is not completely recessive and that it should be possible to detect the heterozygous state in some of the women prior to childbearing. The differences between classical hemophilia and this mild hemophilia have led us to postulate the existence of an allelic mutant responsible for the mild disease. It is proposed that this allele of the normal dominant gene, H, and the classical hemophilia allele, h, be designated h^m. It is possible that there are other alleles, dominant and recessive, which are part of this series of multiple allelomorphs.

We desire to express our appreciation to Mrs. Oliver McFalls for arranging interviews with the members of this family, and to Dr. Maurice Whittinghill of the Zoology Department and Dr. Bernard Greenberg of the Department of Biostatistics for their helpful suggestions.

REFERENCES

1. **Brinkhous, K. M.:** Proc. Soc. Exp. Biol. & Med., **66,** 117, 1947.
2. **Brinkhous, K. M.,** and **Graham, J. B.:** Science, **111,** 723, 1950.
3. **Brinkhous, K. M., Morrison, F. C., Jr.,** and **Muhrer, M. E.:** Federation Proc., **11,** 409, 1952.
4. **Buckwalter, J. A., Blythe, W. B.,** and **Brinkhous, K. M.:** Am. J. Physiol., **159,** 316, 1949.
5. **Davenport, C. B.:** Genetics, **15,** 401, 1930.
6. **Dreskin, O. H.,** and **Rosenthal, N.:** Blood, **5,** 46, 1950.
7. **Dunn, D. B.,** and **Lyons, R. N.:** Med. J. Australia, **2,** 183, 1951.
8. **Graham, J. B., Buckwalter, J. A., Hartley, L. J.,** and **Brinkhous, K. M.:** J. Exp. Med., **90,** 97, 1949.
9. **Graham, J. B., Collins, D. L., Jr., Godwin, I. D.,** and **Brinkhous, K. M.:** Proc. Soc. Exp. Biol. & Med., **77,** 294, 1951.
10. **Haldane, J. B. S.:** J. Genetics, **31,** 317, 1935.
11. **Israels, M. C. G., Lempert, H.,** and **Gilbertson, E.:** Lancet, **1,** 1375, 1951.
12. **Ivy, A. C., Shapiro, P. F.,** and **Melnick, P.:** Surg., Gynec., and Obst., **60,** 781, 1935.
13. **Langdell, R. D., Graham, J. B.,** and **Brinkhous, K. M.:** Proc. Soc. Exp. Biol. & Med., **74,** 424, 1950.
14. **Langdell, R. D., Wagner, R. H.,** and **Brinkhous, K. M.:** Federation Proc., **11,** 420, 1952.
15. **Lee, R. I.,** and **White, P. D.:** Am. J. Med. Sci., **145,** 495, 1913.
16. **Merskey, C.:** J. Clin. Path., **3,** 301, 1950.
17. Idem: Brit. Med. J., **1,** 906, 1951.
18. Idem: Quart. J. Med., **20,** 299, 1951.
19. **Mersky, C.,** and **Macfarlane, R. G.:** Lancet, **1,** 487, 1951.
20. **Nygaard, K. K.:** Proc. Staff Meet., Mayo Clinic, **8,** 365, 1933.
21. **Owren, P. A.:** The Coagulation of Blood, Oslo, J. Chr. Gundersen, 1947, p. 82 ff.
22. **Quick, A. J.:** Am. J. Clin. Path., **10,** 222, 1940.
23. **Smith, H. P., Warner, E. D.,** and **Brinkhous, K. M.:** J. Exp. Med., **66,** 801, 1937.
24. **Wallis, W. A.:** Econometrika, **10,** 229, 1942.
25. **Ware, A. G.,** and **Seegers, W. H.:** J. Biol. Chem., **172,** 699, 1948.

NOCTURNAL CRAMPS IN DIABETES MELLITUS:

CLINICAL AND PHYSIOLOGICAL CORRELATIONS

By CHARLES R. SHUMAN, M.D.

ASSOCIATE IN MEDICINE, TEMPLE UNIVERSITY
SCHOOL OF MEDICINE AND HOSPITAL
PHILADELPHIA, PENNSYLVANIA

NOCTURNAL cramps occurring in the calf muscles and small muscles of the feet have been encountered in a significant number of diabetic patients. The underlying causes of this symptom have not been elucidated despite the accumulating newer knowledge of muscle chemistry and physiology. Because of the remarkable results obtained by the use of quinine in the treatment of this symptom as described by Moss and Hermann[13,14], a careful evaluation was made of a group of 30 diabetic patients complaining of leg cramps in an effort to learn more about this condition.

Almost invariably, this distressing symptom appears at night after the patient has retired; rarely, it may occur while he is resting during the day. It is manifested as an intense, painful contraction of the muscle, usually unilateral, which most frequently awakens him from sleep in the early morning hours. In some, it occurs shortly after getting into bed. In the latter patients, precipitation of the cramp has been recognized by changing positions or by stretching of the muscle in which a contraction subsequently occurs. The usual reaction is to get out of bed and stretch the muscles by walking or by massage of the afflicted parts. Muscular activity does not initiate the pain as is seen in the claudication pain of arterial insufficiency. Certain patients have noted that nocturnal cramps are more frequent after a day of unusual activity. However, this is not uniformly true, as we have encountered this symptom in non-diabetic patients whose activities are restricted because of coronary insufficiency or rheumatoid arthritis.

Although the present report deals largely with diabetics, nocturnal cramps have been found to be common in other groups of patients. In the latter half of pregnancy, leg cramps may become a prominent complaint and have been variously attributed to venous obstruction, thiamine deficiency and pressure of the fetus on the sciatic nerve. Tetanic contractions of the muscles may be encountered in healthy individuals after periods of exertion or in association with fatigue. Gootnick[7] states that rheumatoid arthritis was the commonest precipitating factor in a group of older patients with nocturnal cramps. In the study of Nicholson and Falk[17] of young men with this complaint, static foot deformity was found in 50% to be a possible cause. Interestingly, these symptoms are uncommon in association with arterial insufficiency of the extremities[1]. The nocturnal muscular cramps described in all the above conditions, including pregnancy, seem to be the same as those found in the diabetic where the incidence is striking. Fifty percent of the patients reported by Moss and Herrmann were diabetic[14].

Materials and Methods. The patients described in this report have been examined in the Diabetic Clinic, the diabetic service of Temple University Hospital and in private practice. The records of other clinics wherein these complaints might be encountered

were not scrutinized, so that the overall incidence of leg cramps cannot be evaluated. A total of 30 patients was found in whom the complaint was of sufficient intensity and frequency to require treatment. In this group the diagnosis of nocturnal leg cramps was based upon the history and description of the symptoms. No specific physical signs have been found to accompany this condition. Other causes of leg pains such as vascular disease, diabetic neuropathy and avitaminosis, where encountered, did not appear to have any relationship to the occurrence of nocturnal cramps.

The average age of the 30 diabetic patients included in this report was 53 years with a range of 36 to 77 years. The onset of symptoms occurred from 6 months to 11 years after the discovery of diabetes. In several instances, the patients could recall having had similar symptoms many years prior to the onset of diabetes. One man, 42 years of age, had frequently experienced identical muscle cramps after engaging in competitive sports in high school at the age of 15 years. In 2 patients, the diagnosis and treatment of diabetes was established less than 6 months prior to the onset of severe muscle cramps.

All of the patients were instructed in the Food Exchange System for the dietary management of diabetes. In those patients receiving weight reduction diets, supplementary vitamin therapy was frequently employed. In general, the diets were liberal in protein and carbohydrate components. Insulin therapy, for control of the blood sugar, was employed in all but seven of this group. The preparations used were NPH, protamine zinc, and combinations of NPH and regular insulins. The evaluation of the degree of diabetic control was made on the basis of fasting blood sugars performed at approximately 6 weeks' intervals and the results of fractional urine sugars done at home by the patients in many instances.

In all of these patients the diagnosis of diabetic neuropathy was considered. The failure to elicit symptoms of numbness, hyperesthesias, and to find changes in vibratory or pain sensation or diminution in deep tendon reflexes excluded this diagnosis in the majority. Several patients manifested neuropathic symptoms as well as nocturnal cramps. In these, the administration of quinine sulphate relieved the leg cramps but did not influence the neuropathy. Vascular disease was found to be present on objective examination in 7 patients; however, none complained of claudication pain or other symptoms of arterial insufficiency. Oscillometry was not performed. Varicose veins, present in 4 patients, had long antedated the onset of leg cramps in each instance.

The administration of quinine sulphate was undertaken in those patients with persistent recurrent complaints. The dosage employed in most instances was 0.3 gm. taken at bedtime for a total of 6 to 10 doses. Several patients required 2 tablets, one during the day in addition to the nightly dose. It has been shown that quinine given orally is rapidly absorbed from the bowel and that a single 0.3 gm. dose will produce blood levels of 2.0 to 8.0 mg. per 100 cc.

Results. As previously reported, quinine administration relieved nocturnal leg cramps in the majority of patients. Complete disappearance of the complaint occurred in 26 of the 30 treated. In those who were benefited, no cramps were noted after the second or third night following the administration of the drug. In some instances, relief occurred after the first dose of quinine; occasionally, mild cramps were experienced for several nights which subsequently disappeared entirely. Some of these patients gave a history of previous episodes of nocturnal cramps lasting for varying periods with spontaneous improvement on no treatment. However they were impressed by the effectiveness of quinine in relieving their present attacks and attributed their improvement to it. Placebo therapy, highly desirable in the evaluation of the effects achieved by any agent, was employed in the form of oral vitamin B_{12}, nicotinic acid, Priscoline and thiamine, none of which was of value in alleviating nocturnal cramps.

Prostigmine was administered to several patients because of its cholinergic action which, it was thought, would increase the frequency of muscle cramps thus permitting controlled observations on the effect of quinine in this condition. However, the administration of Prostigmine did not induce a recurrence of the symptoms. Subcutaneous injection of Prostigmine one hour be-

fore bedtime was ineffective in a hospitalized patient who had previously complained of cramps. Similar results were reported by Moss and Herrmann[13,14] who were the first to employ quinine for night cramps following the report of Kennedy and Wolf[10] of its use in the treatment of myotonia.

per 100 cc.) and negative fractional urine sugars were usually present on insulin doses ranging from 0 to 42 units daily for the group. Five of these patients were managed by diet alone. In 6, the degree of diabetic control was considered fair; 2 of these patients were obese and were treated by dietary restriction only. In 6 others, the diabetic control was poor, with wide fluctuations of the fasting blood sugar and persistent glycosuria despite careful dietary instructions and insulin therapy. The carbohydrate intake for the entire group ranged from 150 to 300 gm. daily

TABLE 1.—DATA ON 30 DIABETIC PATIENTS WITH NIGHT CRAMPS TREATED WITH QUININE

			Diabetic Data			
	Patient	*Age in Years*	*Duration in Years*	*Required Insulin Dose*	*Degree of Control*	*Response of Pain to Quinine*
1.	J. H.	42	4	0	Good	Excellent, prompt
2.	A. W.	47	6	44 PZI & Reg.	Poor	Excellent "
3.	N. J.	77	11	0	Fair	Excellent "
4.	J. R.	55	$\frac{6}{12}$	36 NPH	Poor	Excellent "
5.	W. E.	61	1	20 NPH	Good	Excellent "
6.	N. W.	74	6	12 NPH	Good	Excellent "
7.	A. B.	57	5	10 NPH	Good	Excellent "
8.	N. B.	58	4	20 PZI	Good	Excellent "
9.	J. R.	50	4	32 NPH	Poor	Excellent "
10.	M. E.	60	4	36 NPH	Good	Excellent "
11.	J. L.	61	4	0	Good	Excellent "
12.	N. A.	56	3	10 NPH	Fair	Excellent "
13.	A. L.	61	2	20 PZI	Good	Excellent "
14.	B. G.	44	2	20 NPH	Good	Excellent "
15.	A. C.	65	1	0	Good	Excellent "
16.	V. B.	42	2	8 PZI	Good	Excellent "
17.	B. Y.	61	2	32 NPH	Good	Excellent "
18.	M. H.	54	3	16 NPH	Fair	Excellent "
19.	K. B.	57	2	112 NPH & Reg.	Fair	Partial. (a)
20.	L. R.	42	10	0	Good	Excellent, prompt
21.	E. W.	48	2	94 NPH & Reg.	Fair	Poor. (b)
22.	A. C.	56	2	26 NPH	Good	Excellent, prompt
23.	M. B.	57	$4\frac{6}{12}$	44 NPH	Poor	No response. (c)
24.	J. G.	42	1	42 NPH	Good	Excellent, prompt
25.	E. C.	64	$1\frac{6}{12}$	24 NPH	Good	Excellent "
26.	S. B.	44	6	40 NPH	Poor	Poor. (d)
27.	M. M.	51	2	0	Fair	Excellent, prompt
28.	P. W.	51	7	180 NPH & Reg.	Poor	Excellent "
29.	H. J.	36	$\frac{6}{12}$	0	Good	Excellent "
30.	O. M.	51	3	72 NPH & Reg.	Fair	Excellent "

(a) Intervertebral disc demonstrated by myelogram.
(b) Vascular disease, subsequent bilateral amputation.
(c) Sensitivity to quinine, vertigo, vomiting.
(d) Progressive diabetic neuropathy.

In our cases, neither the factor of metabolic control nor the feeding of liberal carbohydrate diets appeared to influence these symptoms significantly, in contrast to the claims of others[4]. In 18 of the 30 patients, satisfactory fasting blood glucose levels (100 to 150 mg.

except for those on weight reduction diets which provided 120 gm.

FAILURES. Among the 4 patients who failed to be benefited by the use of quinine, one was found subsequently to have a herniated lumbar vertebral disc by myelography. She had acknowledged partial relief of nocturnal leg pain during quinine therapy but continued to have symptoms which led to more thorough investigation with disclosure of the neurological complication. Another patient with nocturnal pain in the calf muscles not eased by quinine has, during the past 2 years, required amputation of both legs as a result of occlusive vascular disease. A third patient, incorrectly diagnosed as having nocturnal cramps, has subsequently manifested typical changes associated with diabetic neuropathy which have partially responded to the use of Vitamin B_{12}. The last patient to show no response to quinine proved to be sensitive to small doses of the drug as manifested by vertigo, tinnitus and vomiting, so that treatment was not adequate.

The duration of relief in the 26 patients benefited by quinine has usually been of long-standing. One patient, whose work requires standing for long periods, experienced a severe recurrence of cramps lasting for several nights 2 months after his first episode. This recurrent attack disappeared after the first dose of quinine. Two other patients have noted mild cramping sensations in their calf muscles 6 and 10 months after the treated episode but did not report this until questioned about recurrent symptoms. The remainder of the 26 patients have had no further discomfort.

Discussion. The clinical description of nocturnal leg cramps occurring in diabetic patients corresponds closely with that found in other groups. In diabetes mellitus, there is no evidence to indicate that this symptom is related to the degree of metabolic control or to the duration of the disease. Diabetic control was considered to be satisfactory in the majority of patients included in this report and the symptom appeared in recently diagnosed cases as well as in patients who had been under treatment for many years. No correlation could be found between leg cramps and the weight of the patient or the presence of vascular or neurologic complications of diabetes. Ten patients were found to be 15% or more overweight and 4 were more than 10 pounds underweight. The majority were within a satisfactory weight range. Clinical evidences of peripheral arteriosclerosis were present in 7 patients. In 5 others, objective findings of diabetic neuropathy were noted. However, in those patients with neuropathy, arterial insufficiency or varicosities, treatment of these factors did not alleviate the leg cramps, whereas the use of quinine resulted in their disappearance.

These data do not permit any conclusions concerning the incidence of muscle cramps in diabetic patients. Those included in this report were derived from several sources totalling approximately 400 patients, not all of whom have been questioned about the occurrence of this symptom. Recently, direct questioning indicates that nocturnal leg cramps are far more common than previously realized. One patient, not included in the presentation, stated that she has had severe night cramps which produced weakness of the leg muscles for several weeks after their subsidence. In this patient, as in those presented, the administration of quinine successfully counteracted the condition.

The curariform action of quinine in relieving muscle cramps was suggested by the observations of Kennedy and Wolf[10] who demonstrated the antagonism of this drug to the tetanic contractions seen in myotonia. It was subsequently shown that quinine aggra-

vated the symptoms of muscle weakness seen in myasthenia gravis. The action of quinine appears to resemble that of curare in that it decreases the ability of muscle to respond to repeated stimulation; however, it does not prevent the contraction produced by a single stimulus[2,18]. Quinine produces a refractory state in skeletal muscle similar to that noted in cardiac muscle exposed to quinidine; according to Harvey[8,9], quinine appears to influence both the muscle cell and the myoneural junction in producing this refractory state. He observed that following the administration of quinine the ability of muscle to respond to a tetanus was diminished due to the increased refractory period and that the response to injected acetylcholine was abolished due to the curariform effect of the drug.

Burn[3] has reviewed the chemical transmission of nerve impulses to muscle in stimulating the motor end plate to produce muscular contraction. Tissue activity is under the control of local hormones (acetylcholine, epinephrin and histamine) which act upon receptors present in the cells. These receptors can be made inaccessible to the local hormones by various inhibitors such as quinidine, quinine, atropine, procaine and Benadryl which compete for them and inhibit or abolish the action of the transmittor substances. Thus, if quinine were administered to a patient with muscle cramps or myotonia, acetylcholine would presumably be blocked from its site of action upon the cell because of the presence of quinine. In addition, quinine may have a direct curariform action upon the affected cells.

The failure of Prostigmine, which prevents the destruction of acetylcholine by choline esterase, or of acetylcholine and Mecholyl to accentuate the muscle cramps is not explained. It is known that an increase in the K/Ca ratio favors the cholinergic effect and is associated with increasing muscle irritability as the calcium concentration decreases. Potassium is required for the formation and release of acetylcholine[15]. In this connection, it is interesting to note that muscle cramps and tetany are alleviated by the use of calcium salts[1] which, in effect, lower the K/Ca ratio and reduce muscular irritability. We have not employed calcium in the treatment of our patients; however, it has been found to be satisfactory for the control of certain cases seen in association with pregnancy. In more severe cramps associated with pregnancy, quinine has been used successfully. Diphenhydramine[16] has been recommended for use in pregnant patients with leg cramps in order to avoid the oxytocic effect of quinine upon the gravid uterus.

The sustained contraction of muscle responsible for the cramps may be partially explained by the studies of Szent-Györgyi and others[5,12,19] which indicate the probable manner whereby chemical energy derived from cellular metabolism is transformed into mechanical energy. It is believed that the state of relaxation of muscle is an active process during which energy is stored in the muscle protein-adenosine triphosphate complex. The muscle fibers and their constituent molecules are aligned in an extended position with repellent ionic forces along the polarized membranes maintaining separation and elongation of the parts. With depolarization or excitation of the membrane, the molecules of myosin and actin unite and fold to produce contraction with stored energy being converted into work or increased muscle tension. When muscle becomes fatigued or when oxidative metabolism becomes insufficient, the relaxation phase is slowed, rather than the contraction phase. Thus fatigued muscle displays a high degree of tonicity.

In order to resume the high-energy containing state of relaxation, energy

must be provided for the reconstruction of adenosine triphosphate. This energy is derived primarily from the oxidative metabolism of food with the production of high energy phosphate bonds. The rephosphorylation of adenosine diphosphate to adenosine triphosphate provides a form of available energy which permits repolarization of the membrane and dissociation of actomyosin into actin and myosin. The muscle fibers are then in a state of relaxation and are possessed of the necessary energy for a new contraction. The energy provided by adenosine triphosphate dephosphorylation is used by the muscle fibers to produce the contraction upon excitation.

Upon stimulation of muscle by nerve impulses through the mediation of acetylcholine[15], adenosine triphosphate is broken down to adenosine diphosphate and a high energy phosphate group which provides contraction energy. The muscle contains a surplus store of phosphate bond energy in the form of creatine phosphate which provides additional bond energy and phosphate groups for the reconstitution of adenosine triphosphate, so that the concentration of the latter substance remains unchanged. Creatine phosphate is reformed from energy provided by cellular metabolism.

Several factors may operate in the etiology of leg cramps. a) The lack of adequate creatine phosphate stores in muscle may result in defective adenosine triphosphate reformation thus depriving the muscle cells of the energy necessary for relaxation. There are some indications that creatine concentration may be suboptimal in diabetics. b) An insufficient degree of oxidative metabolism in muscle tissue may also retard relaxation by reducing the availability of energy for recharging the membrane and thus inhibiting repolarization. c) A third factor may be the lack of glycolytic enzymes in the affected muscle which would result in poor energy formation. There is no evidence at present to support the concept of lowered concentration or failure of activity of these enzyme systems. d) Another essential factor for relaxation of muscle is an adequate concentration of sodium ions. In hyponatremic states, muscle cramps are common, as in "stoker's cramps." A reduction in the Na/K ratio at the cell membrane may be responsible factor here, since potassium will lead to the contraction of muscle which can be relaxed by the addition of sodium[5].

The benefit derived from the use of such agents as quinine or diphenhydramine in the treatment of muscle cramps does not assist in determining where the metabolic defect lies in these patients. However, the fact that quinine actually depresses oxygen consumption by muscle tissue *in vitro*[6] suggests that the difficulty is not that of a failure in oxidative metabolism. These agents probably function as inhibitors of depolarization of the cell membrane by engaging the cell receptors and preventing activation of the cell by acetylcholine[3]. This, of course, does not exclude the possibility that the tetanic contraction was caused by a lack of chemical energy required for relaxation of the muscle. In the presence of these inhibitors the muscle tissue would be more refractory to excitation although normal contraction could occur if adequate stimulus were provided. In fact, conservation of energy stores may permit a more effective contraction to a single stimuli when quinine is present[18].

Thus, if energy stores or metabolic activity necessary to provide energy-rich phosphate bonds were suboptimal, quinine may prevent muscle cramps by preventing muscle response to repetitive neural impulses to muscle by its curariform action or by interfering with neuromuscular transmission at receptor sites on muscle cells or both. However, muscle contraction in response to a more intensive stimulus is not impaired.

The failure of thiamine in correcting the symptom tends to exclude the possibility of hyperpyruvemia as a factor in their pathogenesis. Furthermore, pyruvic acid levels in controlled diabetics are normal. It is difficult to find a single explanation to account for the high incidence of these symptoms in such widely divergent groups of patients as those with diabetes and normal pregnancy. It is probable that different causes are operating in various groups and that the effective therapeutic agents interrupt the disturbance in the manner suggested regardless of the underlying disturbance. An interesting experimental approach to this problem in diabetes is discussed by Lilienthal[11].

Summary. The use of quinine sulphate in the treatment of nocturnal leg cramps was found to be effective in 23 of 30 diabetic patients with this complaint.

1. The occurrence of leg cramps was unrelated to the degree of metabolic control, age or weight of the patient, duration of diabetes, or the level of carbohydrate intake.

2. Treatment directed toward vascular or neuropathic complications found in 12 patients did not relieve their muscle cramps.

3. The administration of quinine, 0.3 gm. orally, at bedtime produced freedom from the symptoms after one or 2 doses. Following the nightly administration of quinine for 7 to 10 doses, no recurrence of muscle cramps within a period of 6 months were noted except in the case of one patient who required further treatment after 2 months.

4. Since the relaxation of muscle depends upon available energy for the unfolding of actin-myosin links within muscle fibers, it is suggested that the defect responsible for muscle cramps may lie in the failure of the formation of chemical energy or in storage of energy within the tissues.

5. Quinine and antihistaminics may prevent tetanic contraction by inhibiting the release of available energy under certain conditions.

REFERENCES

1. **Allen, E. V., Barker, N. W.,** and **Hines, E. A., Jr.:** Peripheral Vascular Diseases, Philadelphia, W. B. Saunders Co., 1946.
2. **Briscoe, G.:** Lancet, **1**, 1151, 1939.
3. **Burn, J. H.:** Physiol. Rev., **30**, 177, 1950.
4. **Collens, W. S.,** and **Boas, L. C.:** The Modern Treatment of Diabetes Mellitus, Springfield, Ill., Charles C Thomas, 1946.
5. **Fleckenstein, A., Brose, W., Canis, H. J.,** and **Förderer, A.:** Arch. Exper. Path. Pharmak., **209**, 235, 1950.
6. **Frontali, N.,** and **Toschi, G.:** Boll. Soc. ital. Biol. Sper., **26**, 568, 1950.
7. **Gootnick, A.:** Arch. Int. Med., **71**, 555, 1943.
8. **Harvey, A. M.:** J. Physiol., **95**, 45, 1939.
9. Idem: J. Am. Med. Assn., **112**, 1562, 1939.
10. **Kennedy, F.,** and **Wolf, A.:** Arch. Neurol. & Psychiat., **37**, 68, 1937.
11. **Lilienthal, J. L., Jr.:** On Certain Aspects of the Physiology of Muscle. The Musculoskeletal System, New York, The Macmillan Co., 1952, p. 72.
12. **Mommaerts, W. F. H. M.:** Phosphate Metabolism in the Activity of Skeletal and Cardiac Muscle. Phosphorus Metabolism, Vol. 1, Baltimore, The Johns Hopkins Press, 1951, p. 551.
13. **Moss, H. K.,** and **Herrmann, L. G.:** J. Am. Med. Assn., **115**, 1358, 1940.
14. Iidem: Am. Heart J., **35**, 409, 1948.
15. **Nachmansohn, D.:** Chemical Control of Nervous Activity. The Hormones II, New York, Academic Press, 1950, p. 515.
16. **Naide, M.:** J. Am. Med. Assn., **142**, 1140, 1950.
17. **Nicholson, J. H.,** and **Falk, A.:** New Eng. J. Med., **233**, 556, 1945.
18. **Ravin A.:** Am. J. Physiol., **131**, 228, 1940.
19. **Szent-Györgyi, A.:** Chemistry of Muscular Contraction, 2nd ed., New York, Academic Press, 1951.

TREATMENT OF POST-PNEUMOENCEPHALOGRAPHIC HEADACHE WITH β-PYRIDYL CARBINOL TARTRATE (RONIACOL TARTRATE)*†

By R. M. N. Crosby, M.D.

(From the Department of Neurosurgery, University of Maryland School of Medicine, Baltimore, Maryland)

Several years after the introduction of pneumoencephalography, Schott and Eitel[23] suggested that the severe sequelae should relegate the procedure to use in the cadaver. This advice was generally rejected, so that now, the injection of radio-opaque gas into the cerebral ventricles and subarachnoid space is one of the most common diagnostic procedures used by neurosurgeons and neurologists. The headache, however, which follows this procedure has caused some concern on the part of those who use it and considerable discomfort to those subjected to it. In many clinics, in order to reduce the duration of the headache, it is the practice to use small amounts of gas and move it about the ventricular system by special positioning of the patient[18]. Others have used different gases to lessen the severity of the sequelae[2]. At the University Hospital better results have been obtained by completely replacing the cerebrospinal fluid with air. By this method not only is satisfactory ventricular filling more frequent, but better visualization of the cerebral subarachnoid space is obtained. There is none of the special apparatus needed as with gases other than air, no loss of the gas by rapid absorption before adequate roentgenograms are made and none of the time consuming trial films or special positions which are necessary with other methods. But the headache following the maximum replacement of cerebrospinal fluid with air is rather severe and frequently prolonged. This project was undertaken to study the action of various drugs in the relief of post-pneumoencephalographic headache, in a search for new therapeutic measures, as well as to better understand the mechanism of the production of the sequelae.

The headache which follows pneumoencephalography is probably of 2 varieties. The first, lasting approximately 24 hours, is a result of the irritant effect of the gas, as evidenced by the pleocytosis in the cerebrospinal fluid[5]. Von Storch *et al.*[27] were able to reproduce severe headache of short duration using minute quantities of air without causing any change in the cerebrospinal fluid pressure. This would explain the relatively short duration of the sequelae when only small amounts of gas are used and the shortening of this period of headache by the inhalation of oxygen as recommended by Schwab, Fine and Mixter[24]. It has been our experience that after total replacement of the cerebrospinal fluid with air, inhalation of oxygen is of little or no help to the patient.

The second type of headache is due to cerebrospinal fluid hypotension and is identical to true post-spinal headache. It is this portion of the sequelae of pneumoencephalography which is encountered only when the "total replacement with air" technique is used

* Aided by the Hoffberger Neurosurgical Fund.
† Roniacol Tartrate furnished by Hoffmann-La Roche Inc., Nutley, New Jersey.

and is the period in which therapy could be of considerable value.

Many methods have been recommended for the treatment of post-spinal headache. Innumerable drugs, ranging from dihydroergotamine[4] to antihistamines[25] have had trials. The continued appearance of new remedies testifies to the inadequacy of present therapy. One of the more successful methods both in experimental[12] and clinical trials[1,6] is the mechanical correction of cerebrospinal fluid hypotension by the intrathecal injection of sterile saline and glucose solutions. But because of the dangers involved and the time consumed, the procedure has not been used extensively. In short, no really satisfactory treatment of post-spinal headache has been devised.

The mechanical correction of cerebrospinal fluid hypotension by the intrathecal injection of sterile fluid is not suitable to the treatment of post-pneumoencephalographic headache. Because of the marked lowering of systemic blood pressure following pneumoencephalography, the use of most vasodilators was thought to be contra-indicated. Roniacol Tartrate, an analogue of nicotinic acid, has been shown to have good vasodilating action in the extremities with no action on blood pressure or heart rate in the therapeutic range, and none of the side effects which make other nicotinic acid compounds so objectionable[16]. Of the many drugs available, Roniacol Tartrate appeared to be the most suitable compound to try first in this study.

Material and Methods. PATIENTS: All the patients used in this study were on the Neurosurgical service of the University Hospital. They were unselected and used in rotation: that is, the first 10 cases served as controls, the next 10 received Roniacol by mouth, the third group of 10 received Roniacol intramuscularly and the remainder were given the drug orally. (A preliminary group of 8 patients was used to check the dosage schedule of the medication, but these are not included in the analysis of the result.) Some patients in the direct rotational scheme were eliminated: those in which a surgical procedure followed within a week of the pneumoencephalogram, all children, one case complicated by thrombosis of some of the branches of the basilar artery, one case in which there was prolonged shock following the air study, 2 cases without appreciable headache following the air injection and 2 cases in which the wrong drug dosage was used.

DRUGS: The patients in the control group received codeine sulfate grains one-half and aspirin grains 10, by mouth, every 4 hours as desired. The treated groups received codeine and aspirin. or Pantopon grains one-third, hypodermically, or nothing, for the first 24 hours and the Roniacol Tartrate 75 to 125 mg. every 3 hours.

PROCEDURE: The patient was placed in a sitting position on the Roentgen-ray table and anesthetized with Sodium Surital or Sodium Pentothal, given intravenously. An 18 gauge spinal puncture needle was introduced into the lumbar theca and the pressure measured with a water manometer. Cerebrospinal fluid was then removed in 20 cc. portions and replaced with an equal quantity of air. The pressure in the subarachnoid space was gradually allowed to equal atmospheric pressure by leaving the needle open to leak cerebrospinal fluid each time the syringe was emptied of fluid and filled with air. When no more cerebrospinal fluid was obtained, the head of the patient was tilted from side-to-side and the neck was alternately flexed and extended. The head movements were repeated several times until no more cerebrospinal fluid could be obtained. The needle was then removed and the patient placed in a recumbent position on the table. Forehead up, forehead down and lateral stereographic roentgenograms were made routinely. Anesthesia was discontinued when the developed films were inspected and found to be satisfactory.

Results. 1. CRITERIA. Because of the gradual disappearance of symptoms over a period of several days it was necessary to make a specific end-point for the purpose of this study. Since the major complaint following pneumoencephalography is headache, and the

object of this study was the relief of this symptom, the patient was considered to be free of sequelae when he could be out of bed without headache of any kind. The only chance for error was in those patients in whom the chief complaint prior to pneumoencephalography was headache; but the number of these patients was small, and when the intensity and character of the headache was the same as before the air study and not influenced by position, the patient was considered to be free of sequelae.

the pneumoencephalogram in either the control or treated group. The control group as stated before was unselected and represents the typical duration of sequelae to which we have become accustomed using the "total-replacement with air" method.

In addition to those shown in the Table, Roniacol Tartrate was given orally to 18 other patients following pneumoencephalography. Using the 38 treated patients as a group, the average duration of headache was 1.7 days with limits of 1 to 3 days. There was

TABLE 1.—SUMMARY OF PERTINENT DATA IN 10 CONTROL AND 20 TREATED PATIENTS

	Control	*Roniacol Tartrate Orally*	*Roniacol Tartrate Intramuscularly*
Age	15–67	21–67	21–71
Male	3	8	6
Female	7	2	4
Anesthesia			
Sod. Pentothal	1	7	4
Sod. Surital	9	3	6
Amount of Air (cc)	90–160	75–200	75–145
Average (cc)	120	130	120
Number cases vomiting after 24 hours	6	1	5
Air Over Cortex			
Normal	5	4	5
Excessive	4	4	5
Focal Excess	1	2	0
Duration of Headache (days)	3–6	1–3	1–3
Average (days)	4.3	1.7	1.8
Side Reactions	—	7 in 4 pts. 0 in 6 pts. (over 180 doses)	2 in 2 pts.* 0 in 8 pts. (over 180 doses)

* Patients complained of burning at site of injection.

None of the patients in this series knew that they were receiving any special medication or that any comparison was being made. Only one patient had been subjected previously to pneumoencephalography and he volunteered the comparison to be discussed later.

2. Comparison of Results. Table 1 shows the comparison of the first 30 patients. The average duration of the headache does not include the day of no difference in the duration of headache because of age, sex, type or amount of anesthetic, amount of air injected, or the amount of air visualized in the cerebral subarachnoid space.

Vomiting was well controlled when Roniacol Tartrate was given orally. But when the medication was given intramuscularly, there was no apparent benefit in this respect when compared to the control group. In 2 patients

treated with the intramuscular form, vomiting persisted after the disappearance of headache and stopped only when the medication was discontinued. This is the only way in which the 2 forms differed in their action.

Following the injection of air, a marked fall in the systemic blood pressure is occasionally seen. In the first 30 patients in this series, one patient was in severe shock following the procedure and in several others systolic pressure was found to be lowered as much as 60 mm. of mercury. The average change was 30 mm., systolic and 15 mm. diastolic. In all patients the blood pressure returned to the pre-operative level within 48 hours. There was no apparent relation between the duration of headache or vomiting and the degree or duration of the lowered blood pressure. Nor did the administration of Roniacol Tartrate affect in any way the return of the blood pressure to the pre-operative level.

One patient (C.A.) in the treated group offered a good example of the effect of treatment with Roniacol Tartrate. He had been subjected to pneumoencephalography in another city 2 months before the procedure was repeated at the University Hospital. In both cases the roentgenograms were identical. The original pneumoencephalogram resulted in 8 days of vomiting and severe headache and he understandably submitted to repetition of the procedure only after considerable persuasion. He was given Roniacol Tartrate orally, vomited only on the first day and was out of bed free of headache on the third day. He asked spontaneously what we used or did that was different from the previous pneumoencephalogram.

3. Drug Reactions. As can be seen from the Table, side reactions were few. Those that occurred were with the first dose or doses of the drug and consisted either of flushing or "dizziness." Three patients on whom the intramuscular preparation was used complained of burning at the site of injection. This and the possible production of vomiting has caused us to use the oral form almost exclusively. It should be noted that it was not necessary with either form of the medication to produce flushing in order to insure a satisfactory result.

Discussion. Roniacol Tartrate (β-pyridyl carbinol tartrate) is an alcoholic analogue of nicotinic acid which in the body is slowly converted to nicotinic acid[28]. This slow conversion probably explains the lack of side reactions even with a dose of 125 mg. intramuscularly every 3 hours. It has no action on cardiac rate or systemic blood pressure in the therapeutic levels and is, therefore, more suited to the present use than quaternary ammonium compounds or imidazoline derivatives. In the rare case of idiosyncrasy to nicotinic acid, the activity of the drug can be completely obliterated by epinephrine. Roniacol Tartrate has been shown to dilate retinal blood vessels[22] and has been reported to be effective in angina pectoris[28].

Although this is not the place to discuss at length the controversy concerning the action of nicotinic acid and some of its derivatives on cerebral circulation, some of the evidence must be presented briefly. Moore[15] in 1940 demonstrated a rise in cerebrospinal fluid pressure in 2 patients and dilatation of pial blood vessels in cats following the administration of nicotinic acid. Loman, Rinkel and Myerson[13] were unable to find any change in the cerebrospinal fluid pressure, cerebral arterio-venous oxygen difference or the size of retinal blood vessels following the injection of large doses of monoethanol amine nicotinate. In the same year, Aring *et al.*,[3] using smaller doses

of nicotinic acid, presented evidence which they interpreted as indicating increased intracranial blood flow. They were unable to produce these changes with nicotinic acid amide. Scheinberg[20], using the nitrous oxide method, was unable to show any change in the cerebral blood flow or the cerebral arterio-venous oxygen difference following the intravenous and intra-arterial administration of nicotinic acid. This investigator was also unable to demonstrate by this method any intracranial effect of stellate ganglion block[21], despite the clinical reports of its effectiveness in some cerebrovascular disorders[10,14,17], and visible change in cerebral vessels following stellate ganglion block[26] and stimulation of the cervical sympathetic chain[8].

It is not possible at this time to detail the precise effect of nicotinic acid on cerebral circulation, but the apparent paradox between clinical results and experimental data is readily explicable. As recorded by Scheinberg[20], nicotinic acid probably has no effect on cerebral oxygen consumption, but the exact meaning of the blood flow figures using the nitrous oxide method is not clear. Scheinberg[20] suggested that the method used by Aring *et al.*[3] does not measure intracranial blood flow, but uses the head as a plethysmograph in which the circulation of the face takes part through the common facial vein. This is not completely correct. In the Ferris[7,19] method used by Aring, the skull acts as a plethysmograph and the displacement of the cerebrospinal fluid by the brain is measured. Retrograde flow from the common facial vein through the internal jugular vein into the cranial cavity would not alter the validity of the result using the Ferris technique as it does in a metabolic or chemical method. As long as the result is not interpreted as actual cerebral blood flow, the Ferris method will reveal the capacity of the intracranial vascular bed whether the afferent supply is pure arterial or, as Scheinberg claims, mixed arterial and venous. Aring and his collaborators, therefore, demonstrated an increase in brain volume which was produced by nicotinic acid and not by nicotinic acid amide (as used by Lowman, Rinkel and Myerson). By what method nicotinic acid produces an increase in brain volume is not known, but it is exactly this action which is desired in the treatment of post-spinal and post-pneumoencephalographic headache. Actually, dilatation of the large cerebral vessels would probably exaggerate this type of headache[12].

To our knowledge the only trial of a nicotinic acid preparation in treatment of headache following pneumoencephalography was made by Goldzieher and Popkin[11]. They reported excellent results with the use of intravenous sodium nicotinate in 2 cases following air studies and 13 cases with post-spinal headache. They stated that the patient must "flush" with each dose. Friedman and Brenner[9] could not repeat the result of Goldzieher and Popkin, but did not test sodium nicotinate in any case of post-pneumoencephalographic or post-spinal headache.

In our hands the administration of Roniacol Tartrate according to a definite schedule resulted in the marked shortening of the morbidity period following pneumoencephalography. It was found in preliminary trials and confirmed by several subsequent errors in administration, that if given within the first 24 hours, the drug did not shorten the period of headache or vomiting. This tends to confirm the theory set forth previously that there are 2 definite stages in the production

of headache following the injection of air into the cerebral ventricles and subarachnoid space.

A word of caution must be inserted at this point. The present series is small, particularly in view of the great controversy which follows the publication of any statement in which cerebrovascular physiology is involved. This report is presented at this time with the specific purpose of stimulating trial of Roniacol Tartrate in other clinics.

Summary and Conclusions. 1. Roniacol Tartrate, an alcohol of nicotinic acid, was used in the treatment of post-pneumoencephalographic headache.

2. Favorable results, in comparison to 10 control patients, were obtained in 38 cases when the medication was begun 24 hours after the injection of air.

3. Only 9 instances of flushing or "dizziness" were encountered in over 360 doses and there was no effect upon systemic blood pressure or cardiac rate due to the medication.

4. The possible mode of action of the drug in the relief of post-pneumoencephalographic headache has been discussed.

NOTE: Although used in too few cases as yet to allow any definite conclusions to be made, it is felt that Roniacol Tartrate is of value in the treatment of neurologic sequelae of cerebral angiography and in some cerebrovascular disorders.

REFERENCES

1. **Aherns, R. E.**: New York State J. Med., **48**, 1495, 1948.
2. **Aird, R. B.**: Arch. Surg. **34**, 853, 1937, and Radiology, **30**, 320, 1938.
3. **Aring, C. D., Ryder, R. W., Roseman, E., Rosenbaum, M.,** and **Ferris, E. B., Jr.**: Arch. Neurol. & Psychiat., **46**, 649, 1941.
4. **Caldwell, W. G.**: West. J. Surg., **58**, 11, 1950.
5. **Davidoff, L. M.,** and **Dyke, C. G.**: The Normal Encephalogram, 2nd ed., Philadelphia, Lea & Febiger, 1946, p. 42.
6. **Davidson, H. H., Hingson, R. A.,** and **Hellman, R. A.**: Arch. Surg., **62**, 540, 1951.
7. **Ferris, E. B., Jr.**: Arch. Neurol. & Psychiat., **46**, 377, 1941.
8. **Forbes, H. S.,** and **Cobb, S. S.**: Brain, **61**, 221, 1938.
9. **Friedman, A. P.,** and **Brenner, C.**: New York State J. Med., **48**, 78, 1948.
10. **Gilbert, N. C.,** and **DeTakats, G.**: J. Am. Med. Assn., **136**, 659, 1948.
11. **Goldzieher, J. W.,** and **Popkin, G. L.**: J. Am. Med. Assn., **131**, 103, 1946.
12. **Kunkle, E. C., Ray, B. S.,** and **Wolff, H. G.**: Arch. Neurol. & Psychiat., **49**, 323, 1943.
13. **Loman, J., Rinkel, M.,** and **Myerson, A.**: Am. J. Med. Sci., **202**, 210, 1941.
14. **Mackey, W. A.,** and **Scott, L. D. W.**: Brit. Med. J., **2**, 1, 1938.
15. **Moore, M. T.**: Arch. Int. Med., **65**, 1, 1940.
16. **Redisch, W.,** and **Brandman, O.**: Angiology, **1**, 312, 1950.
17. **Risteen, W. A.,** and **Volpitto, P. P.**: South. Med. J., **39**, 431, 1946.
18. **Robertson, E. G.**: Further Studies in Encephalography. Melbourne, MacMillan & Co., 1946, p. vii.
19. **Roseman, E., Rosenbaum, M., Aring, C. D.,** and **Ferris, E. B., Jr.**: Arch. Neurol. & Psychiat, **46**, 73, 1941.
20. **Scheinberg, P.**: Circulation, **1**, 1148, 1950.
21. Idem: Am. J. Med., **8**, 139, 1950.
22. **Schriffrin, M. J.**: Personal communication.
23. **Schott, E.,** and **Eitel, J.**: Arch. f. klin. Med., **141**, 16, 1922-23, as quoted by **Davidoff, L. M.,** and **Dyke, C. G.**[5], p. 13.
24. **Schwab, R. S., Fine, J.,** and **Mixter, W. J.**: J. Nerv. & Ment. Dis., **84**, 316, 1936.
25. **Shannon, T. R.**: New York State J. Med., **50**, 1259, 1950.
26. **Volpitto, P. P.,** and **Risteen, W. A.**: Anesthesiology, **4**, 403, 1943.
27. **Von Storch, T. J. C., Secunda, L.,** and **Krinsky, C. M.**: Arch. Neurol. & Psychiat., **43**, 326, 1940.
28. **White, S. M.**: Minn. Med., **33**, 133, 1950.

ELECTROLYTE ABNORMALITIES OF THE SWEAT IN FIBROCYSTIC DISEASE OF THE PANCREAS*

By Robert C. Darling, M.D.
PROFESSOR OF PHYSICAL MEDICINE AND REHABILITATION

Paul A. diSant'Agnese, M.D.
ASSISTANT PROFESSOR OF PEDIATRICS

George A. Perera, M.D.
ASSOCIATE PROFESSOR OF MEDICINE
AND

Dorothy H. Andersen, M.D.
ASSISTANT PROFESSOR OF PATHOLOGY

(From the Departments of Physical Medicine and Rehabilitation, Pediatrics, and Medicine, Columbia University College of Physicians and Surgeons and the Presbyterian Hospital, New York, New York)

The abnormally high incidence of heat prostration in children with fibrocystic disease of the pancreas was reported by Kessler and Andersen[2] from observations during a severe heat wave. From the data they present, the mechanism of this susceptibility is not fully explained.

The symptoms of dehydration and vasomotor collapse, which are fairly regular in their series, are not pathognomonic of any of the several mechanisms which produce heat casualties. Only one of their patients showed extreme hyperpyrexia, this one arriving at the hospital bundled in a heavy blanket and having probably a terminal bacteremia. It should be noted that their patients collapsing in the heat were relatively free of symptoms of fibrocystic disease. Among the laboratory data on their patients, the 2 serum chloride values reported are both markedly lowered, one to a value of 59 mEq./L.

Although none of the possible mechanisms for collapse can be excluded from their data, there are some indications toward likely avenues of investigation. Excessive loss of fluids and electrolytes from the gastrointestinal tract could lead to dehydration and hypochloremia, but the patients' clinical histories do not emphasize the symptoms which would be expected in such a mechanism. Pulmonary infection and dysfunction might well contribute to the picture but could scarcely be the sole cause. Adrenal insufficiency must be mentioned as a possible cause of salt loss and shock. There is no confirmatory clinical evidence of this in patients with fibrocystic disease.

Disturbance of the sweating mechanism offers an avenue of explanation which can be explored. Theoretical support is given to this approach by the postulate that the disease is a disturbance of many glandular tissues. Since the children reported were sweating freely and showed no extreme pyrexia, the mechanism is obviously not that of uncomplicated heat stroke in which cessation of sweating and

* This work was supported in part by a grant to Columbia University from the Baruch Committee for Physical Medicine and in part by a gift for Celiac Research from the United Fruit Company.

hyperpyrexia are the distinguishing characteristics. If the collapse were an expression of simple dehydration from excessive sweating, it is difficult to explain the high incidence of heat prostration in cases of fibrocystic disease as compared with other children. A third possible mechanism of disturbance via the sweat glands might depend on an abnormal content of NaCl or other electrolytes in the sweat of these patients. Therefore, the first step of investigation undertaken was to measure and analyze sweat samples in children with fibrocystic disease.

Methods. Subjects for this portion of the study were 9 patients with proven fibrocystic disease in the age group of 5 to 12 years. Two of these patients had had extensive studies of pulmonary function which indicated no measurable disturbance in this area. For controls, 8 children of the same age group were chosen, either normal or recovering from rheumatic fever, nephritis, an asthmatic episode, and so forth. No patient or control was used who was receiving salicylates, ACTH or cortisone.

Each patient was subjected to a standard thermal stress, lying quietly in a room maintained at 89° ± 1° F. and 50 ± 10% relative humidity. Each of the subjects was covered with a standardized sheet and blanket.

Sweat was collected by a method described by one of us[1]. It consisted of the application of a dry gauze square to an area 2 x 3 inches, which was in turn covered by a patch of vaporproof impermeable plastic fabric. The patch was sealed at the edges by waterproof adhesive tape, and maintained in place for one to two hours. At the end of the collection period the patch was lifted and all visible moisture removed by the gauze square; the gauze was immediately placed in a stoppered flask which had been previously weighed with the dry sponge. The flask with the sweat-soaked gauze was then reweighed. To the flask was added a measured volume of distilled water (or $LiSO_4$ [NaCl-free] 200 p.p.m.) and, after leaching, aliquots analyzed for Cl by the method of Keys[3], and for Na and K by flame photometer. Several sites for the collection of sweat were tried; it was found that the abdominal area tended to give more constant yields in a given individual and was technically more suitable, especially in young children.

Rectal temperature was continually observed with an electrical indicating thermometer in all the patients with fibrocystic disease and in several of the controls. No significant elevation in these readings was observed.

Results. The amount of sweat collected per unit of surface and time was found to be extremely variable in both the patients and the controls, and no trend or significant difference was observed. Likewise, with this standardized thermal stress there was no correlation in either group between the amount of sweat and the chloride concentration.

The analytical results for chloride, and in some cases for sodium and potassium, are indicated in Table 1. It is apparent that for this standardized thermal stress, which is actually mild, the chloride concentration of the sweat in the fibrocystics was more than three times that in the control subjects. When measured, the sodium was somewhat higher than the chloride, which is in line with previous observations that the sweat is a solution of relatively neutral pH containing principally sodium chloride as its electrolyte constituent.

Discussion. Observation of a relatively high sodium chloride concentration in sweat is an unexpected finding in fibrocystic disease, quite unrelated to the previously recognized clinical abnormalities. However, it offers a reasonable explanation of the susceptibility to heat casualty which these patients show. Within the last month 3 new heat casualties have been observed among patients with this condition during a recent 3-day heat wave. Incidentally, these were the only patients admitted to the hospital during this period with illness apparently due to hot weather alone.

One of these, the most severely ill, S. H., age 3 7/12th years, presents an illuminating history. It is stated that during the 2 days of severe heat he

perspired freely and for the first day was very thirsty and drank much water. In the middle of the second day he began to feel below par and near the end of the second day he began to vomit. During the next 12 to 15 hours he went gradually downhill, vomited several more times, and finally lapsed into coma. He was admitted to the hospital in deep coma and severe shock. He was treated with intravenous sodium chloride and plasma; a blood sample taken an hour after the start of treatment showed a serum sodium of 127 mEq./L. and chloride of 79 mEq./L. He rapidly recovered from his dehydration and shock. The next morning the sodium was 134, the chloride 94. At this time the NPN was 118 mg. per 100 cc., his urine showed albumin and red cells. The renal picture cleared in three days and the NPN fell to 34 mg. per 100 cc.

The other 2 patients were not admitted until 2 days after the hot spell had ameliorated but their difficulty began with a similar though milder picture during the period of heat. The vomiting and inability to take fluids, however, persisted, and they were admitted afebrile in moderate vasomotor collapse and dehydration. In both, the serum chloride was low on admission and returned to normal with therapy.

Preliminary results on 2 patients with fibrocystic disease, admitted to the metabolic ward for studies on a constant fluid and dietary regimen, throw further light on the subject. Both the patients had a constantly high salt concentration in their sweat, as determined by the technique described above. This was true even during a period of low salt intake (15 mEq. per day). One was able to reduce his urinary sodium excretion to very low values (<5 mEq./24 hours) on hot days. In spite of similar renal retention of salt, the other test subject after 4 days of salt restriction in warm weather showed a reduction in serum sodium from 138 to 131 mEq./L. and in serum chloride from 101 to 90 mEq./L. and developed a definite hemoconcentration. The stool

TABLE 1.—ELECTROLYTE CONCENTRATIONS IN ABDOMINAL SWEAT OF PATIENTS WITH FIBROCYSTIC DISEASE AND CONTROLS OF THE SAME AGE GROUP

Diagnosis	*Subject*	*Chloride mEq./L.*	*Sodium mEq./L.*	*Potassium mEq./L.*
Fibrocystic Disease	L. F.	78		
" "	G. D.	109		
" "	R. C.	131		
" "	L. F.	98		
" "	A. B.	91		
" "	V. D.	73	97	17.2
" "	S. H.	124	136	16.0
" "	C. J.	130	119	17.2
" "	M. T.	87	87	12.8
	Mean ± SDM	102 ± 7.4		
Control—Nephritis	R. S.	34		
" Normal	T. D.	22		
" Erb's Paralysis	F. C.	22		
" Postoperative Hernia	W. H.	24		
" Primary Tuberculosis	E. H.	16		
" Asthma	W. D.	18		
" "	P. K.	42		
" Rheumatic Fever	J. H.	33		
	Mean ± SDM	26 ± 3.2		

sodium was regularly low; the stool potassium was high but the total balance of potassium was positive. An eosinopenic response and a rise in 17-ketosteroid excretion followed the repeated injection of ACTH over a 48-hour period in 2 subjects tested.

It is evident that the fibrocystic patient in hot weather has difficulty in retaining salt via the sweating mechanism. The early clinical symptoms are not dissimilar to those ascribed to the salt deprivation syndrome as observed clinically and to those induced experimentally by McCance[4]. Unlike normal individuals, these children cannot lower markedly the concentration in their sweat during the period of salt lack, as was seen in 2 patients subjected to balance studies. However, these patients and presumably the others had an efficient renal mechanism for the conservation of salt. It seems probable that difficulty ensues only when salt loss in the sweat exceeds the intake.

The subsequent clinical development in the histories of the heat casualties was apparently that of superimposed dehydration related to vomiting and poor intake. The moderate fever observed was that presumably of dehydration, particularly since in S. H. the temperature returned promptly to normal after treatment.

The efficient retention of salt by the kidneys in one patient, both in response to hot weather and to curtailment of dietary salt, as well as the response to ACTH administration, are strong evidence against any salt disturbance involving the adrenal cortex. The fact that sweat glands do not retain salt efficiently in hot weather suggests that the disturbance lies in the sweat glands themselves.

The therapeutic implication of these observations would seem to be fairly clear. During hot weather patients with fibrocystic disease should be instructed to take more salt than other children.

Summary and Conclusion. 1. Nine patients with fibrocystic disease of the pancreas showed a markedly higher concentration of chloride in sweat from the skin of the abdomen than did a comparable group of controls.

2. Clinical observations among heat casualties with fibrocystic disease are in accord with the concept that the primary mechanism of their susceptibility lies in excessive salt loss in the sweat.

3. Preliminary studies on fibrocystic patients under controlled conditions indicate that renal mechanisms of salt retention are normal, that the gastrointestinal tract is not the avenue of excessive salt loss, and that no primary adrenal dysfunction is present.

4. By exclusion, the cause of the excessive salt loss in the sweat probably lies in the sweat glands themselves, a new site for possible abnormality in this disease.

REFERENCES

1. **Darling, R. C.:** Arch. Phys. Med., **29,** 150, 1948.
2. **Kessler, W. R., and Andersen, D. H.:** Pediat., **8,** 648, 1951.
3. **Keys, A.:** J. Biol. Chem., **119,** 389, 1937.
4. **McCance, R. A.:** Proc. Roy. Soc. London, **119,** 245, 1936.

RHEUMATOID ARTHRITIS THERAPY: A RATIONALE AND THE USE OF CHLOROQUINE DIPHOSPHATE*

By GEORGE GREGORY HAYDU, M.D.
CONSULTANT-IN-ARTHRITIS, HUNTINGTON REHABILITATION
HUNTINGTON, L.I., NEW YORK

IT was suggested[19], even before the use of cortisone, that rheumatoid arthritis is based on the high effort level of the tissues, especially for adenosintriphosphate (ATP) and a simultaneous lack of hormonal support. Evidence for such a view was based on data concerning glucose utilization in rheumatoid and control cases, where tissue ATP was regenerated[21,22]. It was thought further that inhibition of the tissues' requirement for ATP should bring amelioration of many of the symptoms of rheumatoid arthritis. Such was found in the short-term effect of pitressin[20], a characteristic adenosintriphosphatase inhibitor[2]. Gold and copper salts used in the treatment of rheumatoid arthritis are also powerful inhibitors of ATP-ase activity[13,14].

Recently, substances in the quinine group were found to have inhibitory effect on ATP-ase activity[48]; at any rate, to have ATP sparing qualities[4]. In addition, polymerization of actin, which requires ATP[31], is also inhibited by quinine[46]. A rationale of therapy of rheumatoid arthritis as described below, indicated further that the molecular configurations of anti-malarial drugs might be utilized in the treatment of rheumatoid arthritis.

Procedure. Chloroquine diphosphate was given to 28 rheumatoid arthritis patients, for 6 months, 0.5 gm., 3 times a week. Six months period of continuous administration of chloroquine produced no toxic effects in any of the patients, as indicated by complete blood counts, urinalysis, and cephalin flocculation tests.

Results. In Table 1, age, sedimentation rates before and after treatment, structural and functional involvement, and classified improvement are indicated for each patient. The last three data follow the criteria suggested by Steinbrocker, Traeger and Batterman[45]. Table 2 summarizes the patients according to the severity of involvement. Table 3 summarizes improvement according to classification of the remissions.

These data show that 21 out of 28 cases exhibited considerable improvement. Only one patient had complete remission and one had no signs of improvement. Considering the length of treatment and the nature of rheumatoid arthritis, these data are not sufficient for judging the true efficacy of chloroquine therapy. At this time, chloroquine might be regarded as one additional antirheumatic substance.

Rationale and Discussion. Rheumatoid arthritis patients undergo long periods of high effort that precede any joint involvement[26,36]. After the period of high effort, there follows a period of exhaustion which is still antecedent to clinical arthritis[19]. A recent British review is quite unequivocal on this point[41]. When effort must be transacted on a high level for a variety of reasons (like too much work and no rest, or living under great psychological stress,

*The part of this paper which deals with the rationale of therapy, was presented in an address at the Second European Rheumatological Congress, Barcelona, Spain, 1951.

or undergoing the high effort requirements of lobar pneumonia, etc.), then, peripheral work required of the tissues is supported by the adrenal cortex. This period of high effort cannot be maintained too long by certain constitutional types[19]. The adrenocortical activity returns to normal or subnormal levels[12] and there develops a relative adrenocortical insufficiency. This period of high effort of the tissues without adequate hormonal support appears clinically as the period of exhaustion.

The increase of effort level of the tissues goes parallel with increased requirement for ATP[8,28,34]. There is also evidence that the maintenance of the proper functioning status of the membranes requires ATP energy[16,33,43]. ATP-ase itself is a lipoprotein[29,47]. Lecithinase activity on Mg ATP-ase proceeds proportionately with the loss of ATP-ase activity[29]. This is in conformity with findings that the function of cells is bound up with the state of the lipid membranes[9,39].

Lipid membranes form a double

TABLE 1.—CLASSIFICATION OF CLINICALLY ACTIVE RHEUMATOID ARTHRITIS PATIENTS RECEIVING CHLOROQUIN DIPHOSPHATE AND CLASSIFICATION OF THEIR IMPROVEMENT AFTER SIX MONTHS OF TREATMENT

				Structural Functional Involvement		*Improvement*
Initials	*Age*	*Sed. Rate Before Treatment*	*Sed. Rate* After Treatment*	*Stage†*	*Class‡*	*Grade^*
I. A.	72	40	36	II.	II.	III.
E. B.	58	16	16	II.	II.	II.
J. B.	57	2	4	II.	II.	II.
G. B.	40	5	3	I.	II.	II.
M. B.	51	35	15	III.	III.	II.
M. C.	37	29	22	II.	II.	II.
A. C.	54	20	23	II.	III.	II.
T. D.	40	22	18	II.	II.	II.
H. E.	62	41	38	III.	III.	III.
F. F.	51	50	29	III.	III.	II.
I. G.	50	32	11	II.	II.	I.
R. H.	61	98	81	III.	IV.	IV.
M. H.	46	23	15	III.	III.	II.
R. K.	38	12	12	II.	III.	II.
G. K.	50	26	20	II.	II.	II.
H. L.	29	31	22	II.	II.	II.
M. L.	62	25	16	III.	II.	II.
M. M.	34	21	14	III.	III.	II.
B. M.	52	24	10	II.	II.	II.
M. M.	54	32	30	II.	II.	II.
M. P.	64	6	8	II.	III.	II.
A. P.	52	62	49	III.	III.	II.
J. P.	78	15	16	I.	II.	II.
B. R.	41	52	42	III.	III.	III.
A. S.	36	39	40	III.	III.	III.
G. T.	65	84	51	III.	II.	II.
A. V.	58	64	32	III.	III.	II.
M. W.	61	18	13	II.	II.	III.

†Stage I: Osteoporosis, II: Slight destruction, Swellings, No deformities, III: Considerable destruction, Deformities, IV: Ankylosis

‡Class I: Complete function, II: Handicapped but adequate, III: Very much limited, IV: Largely incapacitated.

^Grade I: Complete remission, II: Minimal residual joint swelling, etc., III: Decreased symptoms, IV: Unimproved.

*Westergren Method

layer of rods around all the functioning elements of the cells[11,25,30,40]. Experimentally, Clowes could show[7], that monomolecular films of phospholipids and cholesterol, in the proportion in which they occur naturally, can bind many chemically inert but physiologically potent substances, like carcinogenic hydrocarbons. Alteration of lipoprotein membranes governs, in the last analysis, permeability[10]. Thus hemolytic fatty acids[3], anesthetic drugs[35] exert their effect in proportion to their lipid solubility. In turn, cholesterol can reestablish some of this disturbed balance[27,32]. Adlineation of a molecule to the surface films is of great importance as to how physiologically and how selectively a hormone, or a drug can exert its effect. Steroid substances are completely adlineated to the indispensible cholesterol part of the tissues' lipoprotein configurization.

TABLE 2.—SUMMARY OF PATIENTS ACCORDING TO STRUCTURAL AND FUNCTIONAL CLASSIFICATION OF JOINT INVOLVEMENT

Structural Involvement	*Functional Involvement*	*Number of Patients*
Stage	*Class*	
I.	II.	2
II.	II.	11
II.	III.	3
III.	II.	2
III.	III.	9
III.	IV.	1

Most biologically active steroids carry hydroxyl or keto groups on the inner surface of the steroid structure. It is through these polar groups that cortisone, or desoxycorticosterone increases the membranes' permeability for potassium and increases, thus, the effort level of the tissues. Such hydroxyl or keto groups can exert their effects physiologically, once they are selectively carried by the steroid configurization upon the membrane. Even in the case of the hemolytic activities of bile acids, oxidation of the hydroxyl groups reduces the membrane penetrating activity as well as the lytic properties of these steroids[17]. The blocking of the hydroxyl or keto groups with methyl or methoxy groups should facilitate the reduction of effort level of the tissues. Methyl groups impart greater resistance to depolarization and thus the high ATP requirement of rheumatoid arthritis may be reduced. In this respect a recent report of the First Annual Steroid Conference is interesting[19]: among 12 assorted steroid substances only one showed antirheumatic activity. This was the only substance which instead of hydroxyl or keto formation at C3 had an acetoxy group.

TABLE 3.—SUMMARY OF PATIENTS ACCORDING TO CLASSIFICATION OF IMPROVEMENT

Improvement Grade	*Number of Patients*
I. (Complete)	1
II. (Major)	21
III. (Minor)	5
IV. (None)	1

The steroid form may not be necessary. Molecules which fit less perfectly can also be counted on if they bear the methyl or methoxy group strategically and block in this way the high effort activity of rheumatoid arthritis. Apart from what was cited previously[4,46,48], there is circumstantial evidence that quinine and quinacrine act in this manner. The degradation of quinine in the body attaches hydroxyl groups to the inner surface and with it goes loss of the specific activity[44]. A similar change occurs with quinacrine[18].

Cortisone administration in rheumatoid arthritis supports the high effort

level of the tissues, but once discontinued, the rheumatoid process returns. Desoxycorticosterone increases the effort permeability of membranes[24], but does not increase the deamination of amino-acids and through them those oxidative processes which produce generous ATP production in the case of cortisone[6,15]. Thus, desoxycorticosterone can produce lesions in animals which resemble rheumatoid arthritis[42]. We noticed repeatedly, that desoxycorticosterone administered alone to rheumatoid arthritis patients brought about an aggravation of their condition. In collaboration with Dr. Youngwirth[23] we found further that progesterone, which has a desoxycorticosterone-like action, produces also an aggravation of the rheumatoid process even if it imparts temporary strength to the patients. In fact, anything which increases the requirements for ATP without increasing hormonal support will worsen the rheumatoid condition. Substances of the cell nucleus increase ATP requirements[38] and we found that injections of Pentnucleotide produced a very prompt aggravation of rheumatoid arthritis.

Since the writing of this paper, quinacrine was employed in the treatment of lupus erythematosus[37], and Primaquine in the treatment of rheumatoid arthritis[5]. We found Primaquine in a preliminary study, inferior in antirheumatic activity to that of chloroquine.

Since the writing of this paper there also appeared a study[1] on the pharmacological action of Benemid, another antirheumatic substance. The study concluded that Benemid acts by "inhibiting a definitive enzyme, that requires a source of 'high phosphate bond' energy for the completion of at least one reaction involved." This again is in good accord with our rationale outlined above.

The reduction of the high effort level of the tissues of rheumatoid patients is the aim of therapy. The pharmacological approach may not be the only one. The causes which bring about the high effort level can also be dealt with. This, however, must be the subject of a different study.

Summary and Conclusions. 1. With the view of inhibiting the tissues' requirements for ATP, choloroquin was used therapeutically in rheumatoid arthritis.

2. Three times weekly, 0.5 gm. was administered to 28 patients for 6 months without toxic effects.

3. Twenty-one patients improved considerably, one patient had complete remission, one did not improve.

4. A view of rheumatoid therapy was offered which finds biochemical rationale for the use of chloroquine, gold, cortisone, and other antirheumatic agents.

REFERENCES

1. **Beyer, K. H., Russo, H. F., Tillson, E. K., Miller, A. K., Verwey, W. F., and Gass, S. R.:** Am. J. Phys., **166**, 625, 1951.
2. **Binkley, F.:** Science, **109**, 88, 1949.
3. **Bodansky, M. J.:** J. Biol. Chem., **79**, 241, 1928.
4. **Bovarnick, M. R., Lindsay, A., and Hellerman, L.:** Ibid., **163**, 535, 1946.
5. **Brennecke, F. E., Alving, A. S., Arnold, I., Bergenstal, D. M., and DeWind, L. T.:** J. Lab. & Clin. Med., **38**, 795, 1951.
6. **Cagan, R. M., Gray, J. L., and Jensen, H.:** J. Biol. Chem., **183**, 11, 1950.
7. **Clowes, G. H. A.:** Publ. 21., Am. Assn. Adv. Sci., 1943.
8. **Csapo, A.:** Nature, **162**, 218, 1948.
9. **Danielli, J. F., and Adams, N. K.:** Biochem. J., **28**, 1583, 1934.

10. **Danielli, J. F., and Davis, N.:** Adv. Enzymol., **2,** 87, 1950.
11. **Davson, H., and Danielli, J. F.:** Permeability of Natural Membranes. New York, Macmillan Co., 1943.
12. **Dobriner, K.:** Bull. Rheum. Dis., **2,** 5, 1951.
13. **Forestier, M. J.:** Bull. et mém. Soc. méd. d. Hop. de Paris, **45,** 323, 1929.
14. **Forestier, M. J., and Certonciny, A.:** Rev. Rhum., **14,** 271, 1947.
15. **Friedberg, F., and Greenberg, D. M.:** J. Biol. Chem., **168,** 405, 1947.
16. **Gerard, R. W.:** Ann. New York, Acad. Sci., **47,** 575, 1946.
17. **Grodius, F. S., Berman, A. C., and Ivy, A. C.:** J. Lab. & Clin. Med., **27,** 181, 1951.
18. **Hamick, D. L., and Mason, S. F.:** Nature, **156,** 718, 1945.
19. **Haydu, G. G.:** Am. J. Occ. Ther., **3,** 177, 1949.
20. **Haydu, G. G., and Haydu, B. W.:** Am. J. Med. Sci., **223,** 1, 1952.
21. **Haydu, G. G., and Wolfson, A. H.:** Rheumatism, **6,** 9, 1950.
22. Iidem: Ibid., **6,** 57, 1950.
23. **Haydu, G. G., and Youngwirth, S.:** Unpublished Data, 1945.
24. **Haydu, S., and Szent-Gyorgyi, A.:** Am. J. Phys., **168,** 159, 1952.
25. **Hillarp, N. A., and Olivercrona, H.:** Acta Anat., **2,** 119, 1946.
26. **Howitt, F. D., and Christie, W. F.:** Lancet, **2,** 1282, 1931.
27. **Hsu, F. Y., and Young, L-M.:** Chinese J. Phys., **16,** 189, 1941.
28. **Jaeger, L., and Barth, L. G.:** J. Cell. & Comp. Physiol., **32,** 319, 1948.
29. **Kielley, W. W., and Meyerhof, O.:** J. Biol. Chem., **183,** 391, 1950.
30. **Kiessig, H., Phillippoff, W.:** Naturwiss., **27,** 593, 1939.
31. **Laki, K., and Clark, A. M.:** J. Biol. Chem., **191,** 599, 1951.
32. **Lee, J-S., and Tsai, C.:** Quart. J. Exp. Physiol., **31,** 271, 1942.
33. **Lindberg, O.:** Exp. Cell. Res., **1,** 105, 1950.
34. **Moog, F.:** J. Exp. Zool., **105,** 209, 1947.
35. **Overton, E.:** Studien ueber die Narkose, Jena, 1901.
36. **Osgood, R. B.:** New Engl. J. Med., **204,** 551, 1931.
37. **Page, F.:** Lancet, **2,** 755, 1951.
38. **Potter, V. R., Lyle, G. G., and Schneider, W. C.:** J. Biol. Chem., **190,** 293, 1951.
39. **Redeal, E. K.:** Nature, **144,** 693, 1939.
40. **Schmitt, F. O., and Palmer, K. J.:** Cold Spring Harbor Symp., **8,** 94, 1940.
41. Scient. Adv. Com.: Brit. Med. J., **1,** 800, 1950.
42. **Selye, H., Sylvester, O., Hall, C. E., and Leblond, C. P.:** J. Am. Med. Assn., **124,** 201, 1944.
43. **Shanes, A. M., and Brown, D. E. S.:** Cell. Comp. Physiol., **19,** 1, 1942.
44. **Shannon, J. A.:** Harvey Lectures, **41,** 43, 1946.
45. **Steinbrocker, O., Traeger, C. H., and Batterman, R. C.:** J. Am. Med. Assn., **140,** 659, 1949.
46. **Straub, F. B., Feuer, G., and Lajos, I.:** Nature, **162,** 217, 1948.
47. **Szent-Gyorgyi, A.:** The Chemistry of Muscular Contraction, New York, Academic Press, 1947, p. 84.
48. **Webb, J. L., Saunders, P. R., and Nakamura, K.:** J. Pharm. & Exp. Ther., **101,** 287, 1951.
49. **White, A.:** Symposium on Steroids in Experimental and Clinical Practice. New York, The Blakiston Co., 1951, p. 236.

VITILIGO AND JAUNDICE

By LAMONT E. DANZIG, M.D.*
FORT SAM HOUSTON, TEXAS
(1st. Lt., MC, Surgical Research Unit, Brooke Army Hospital, Fort Sam Houston, Texas)

IT is relatively easy to gather information from the many standard textbooks in dermatology as to the pathologic physiology of the primary dermatologic diseases accompanied by or occurring after pigmentary changes in the skin. However, there is less known regarding the color of the skin in systemic diseases, and not until 1944, when Jeghers[4] published an exhaustive and inclusive summary of the literature, was there a reliable and easily accessible reference to the physiology of systemic coloring.

We have had the opportunity to observe an unusual case of vitiligo and jaundice in which local and systemic pigmentary factors were involved. Their coexistence and resulting effect on the coloring of the skin were extraordinary and warrant the report of this case with a discussion of some of the physiologic and pathologic factors involved. To our knowledge, a similar observation has not been reported in the literature.

Case Report. The patient, a woman 62 years of age, was known to have had marked patches of skin depigmentation characteristic of vitiligo for approximately 40 years. She had been a known diabetic for 20 years and received insulin daily. She had experienced several painless prolonged periods of jaundice several years before admission to the hospital and a tentative diagnosis of cirrhosis was made. Several days before admission to the Evans Memorial Hospital on July 11, 1950, the patient had lapsed into a semistuporous state.

On examination, the patient was found to be poorly nourished, but otherwise well developed. The blood pressure was 150/72. Slight dehydration was present, the respirations were not unusual, and the odor of acetone was not apparent on her breath. The liver was enlarged approximately 5 cm. below the costal margin; it was firm, finely granular, and tenderness was not evident. Neurologic examination was not remarkable except for hypoactive deep tendon reflexes. The remainder of the examination was normal.

The color of the skin was striking. There were large coalescing, sharply demarcated patches of depigmentation of various sizes and shapes covering the face, upper extremities, and trunk. These colorless areas were surrounded by hyperpigmented skin. The scleras, buccal mucosa and all the skin that was not depigmented were icteric. The patches of depigmentation, regardless of their location, were completely white and stood out conspicuously in contrast to the surrounding jaundiced integument. The skin in all areas was moist, smooth, soft, slightly atrophic, nonedematous and devoid of any inflammatory process. The diagnosis of vitiligo was substantiated by a consultant from the Department of Dermatology, but he was unable to offer an explanation for the peculiar distribution of the jaundice.

Glycosuria and hyperglycemia were revealed in the laboratory data. The hemoglobin was 14 gm. per 100 cc., the hematocrit 43%, and the white blood count was 4,600 per c. mm. with a normal differential. The nonprotein nitrogen was 42 mg. per 100 cc., the chlorides, 96.4 mEq./L. and the CO_2 26.4 mEq./L. The prothrombin time was 67% of normal, the alkaline phosphatase 10.3 Bodansky units, the cephalin flocculation 3+ in 48 hours and the thymol turbidity 16 units. The total serum bilirubin was 6.2 mg. per 100 cc. with a direct value of 3.7 mg. per 100 cc. A trace of bile was noted in the urine; the urine urobilinogen was normal. The stools were brown in color.

The patient's course in the hospital progressively deteriorated. She lapsed into a coma and bronchopneumonia developed. The jaundice deepened somewhat, and 4 days before death an icterus index was 100 units. Meanwhile, the distribution of the pigment

* Former Assistant Resident in Medicine, The Robert Dawson Evans Department of Clinical Research and Preventive Medicine, Boston, Massachusetts.

in the skin did not change. The patient died 17 days after admission to the hospital.

The clinical diagnoses, confirmed at autopsy, were bilateral bronchopneumonia, diabetes mellitus (clinical), portal cirrhosis of the liver with jaundice, esophageal varices, splenomegaly, and vitiligo. Identical findings were revealed in the histologic examination of the integument in both pigmented and depigmented areas except for the lack of melanoblasts in the latter.

Discussion. Neither we nor Jeghers[5] are aware of a similar observation having been made. Numerous cases of vitiligo and albinism have been described, but the appearance of the skin has never been recorded if and when it became icteric.

In spite of the voluminous literature on jaundice, there is a paucity of knowledge concerning the manner in which bile pigments impart to the skin the characteristic yellow tinge. This gap in our comprehension of skin pigmentation will be discussed after a brief review of the coloring in normal skin and vitiligo.

NORMAL SKIN. Using a recording spectrophotometer, Edwards and Duntley[3] were able to identify and to study the quantitative distribution of pigments in the normal skin. They found five cutaneous pigments: melanin, a derived material described as melanoid, carotene, reduced hemoglobin, and oxyhemoglobin. The small amount of bilirubin normally present in the blood and tissues does not appear to play a detectable role in the causation of normal skin color.

Melanin is the pigment of particular interest because it is this substance which contributes most to skin color. It is responsible for color effects in the skin varying from yellow through brown to black; thus, it is absent in albinos, has a spotty distribution in people who have vitiligo, is present in the smallest amount in blondes, is more noticeable in brunettes and is present in the largest amount in the darker racial groups[4]. It is formed by melanoblasts, which are specialized cells regularly distributed throughout the basal layer portion of the epidermis. Under certain stimuli, these cells enlarge, become dendritic and form microscopic granules (melanin). The stimuli may represent external factors such as sunlight, artificial ultraviolet rays, Roentgen rays, heat, mechanical and chemical irritations, or it may be concerned with pituitary, adrenal and gonadal activity, with the activity of a number of vitamins (A, C and parts of the B complex) and possibly with the activity of the nervous system[14].

The activating factor in melanin production has not been firmly established and is in some respects controversial. It is postulated that the formation of melanin may be similar to that which occurs in plants, a mechanism which is fairly well established[6,8,14]. In plants, tyrosine is activated by the enzyme tyrosinase through the introduction of a second hydroxide group to form dihydroxy-phenylalanine (dopa). Because of the close structural relationship of epinephrin and tyrosine, it is postulated that in man the adrenal medulla converts tyrosine to epinephrin directly, but that "dopa" may be formed in the process as an intermediate product. If "dopa" is applied to normal sections of the skin, heavy pigmentation is produced; therefore, it is concluded that "dopa" is the precursor of melanin and that the oxidizing enzyme (dopa-oxidase) in the skin itself is responsible for the conversion. It is believed that only melanin-producing melanoblasts contain the oxidizing enzyme.

VITILIGO. Vitiligo is an acquired cutaneous achromia characterized by variously sized and shaped single or multiple patches of milk white color, usually having hyperpigmented borders and a tendency to enlarge peripherally. The only sign in vitiligo is the

absence of pigment-producing color changes. There are no symptoms. The skin is neither elevated nor depressed below the general surface. The patches may be few or numerous and the sites are usually on the face, neck, and backs of the hands. However, the distribution may be more generalized. Textural changes of the skin are not present and with the exception of the affected patches, in which the pigment is completely lacking, the skin is normal in every way[1,11]. It should be noted that systematic investigations have not been undertaken concerning the absence or presence of elastic tissue in the vitiliginous skin (see below), nor have pathologists investigated capillary size in the affected areas. Levy-Frankel, Guillaume, and Juster[9] have observed marked capillary constriction and a paucity of capillaries in the depigmented zone, but this has not been confirmed. In the adjoining hyperpigmented skin, the amount of melanin in the basal layer is increased and numerous melanoblasts are present in the upper corium.

PATHOLOGIC PHYSIOLOGY OF ICTERIC SKIN. The pathogenesis of the yellow coloring of the skin known as jaundice appears to be very simple, but a more thorough consideration of the matter shows that it is rather complicated and very poorly understood. With[17,18] has done more than anyone else to focus attention on this problem and has written extensively in the Scandinavian literature.

To my knowledge a reliable histologic technique for identifying the site of deposition of bilirubin or its allied pigments in the integument of jaundiced skin has not been established; and, equally important, thorough chemical examinations of the colored substances of the icteric skin have not been carried out. Therefore, it is fair to say initially that the nature of the chemical substance deposited is not definitely known, nor is it known whether the pigment is deposited intra- or extra-cellularly.

Accordingly, jaundice could be defined as a yellow coloring of the skin which occurs simultaneously with hyperbilirubinemia and not simply as a result of deposition of bilirubin. For instance, With[18] emphasizes that there are allied yellow compounds such as xanthorubin, bilifuscin and mesobilifuscin, and not bilirubin alone that impart the yellow color to plasma in jaundice, and possibly the same is the case for the skin. These allied compounds do not give the diazo reaction with the use of Ehrlich's reagent, and, therefore, are not measured when a serum bilirubin is performed. This fact probably explains the discrepancy between some icterus indices and serum bilirubin determinations.

It should be remembered also that the small amount of bilirubin normally present in the blood and tissues does not appear to play a detectable role in the causation of normal skin color. Jaundice develops only when the bilirubin concentration reaches a critical level of 1.5 to 2 mg. per 100 cc. in adult white persons.

As With[17] has so ably pointed out, the first consideration should be whether the tissues themselves are colored. Even in severe jaundice the red color of the blood is much more intense than the yellow color of the plasma and yet the skin assumes only a faint red shade of color; therefore, it would appear excluded that the yellow color of the plasma would cause the pronounced yellow color of the skin which is seen in icterus. Furthermore, it is well known that the yellow color of the skin is maintained after most of its blood is removed *in vivo* by compression, and that clinically detectable tissue staining recedes more slowly than plasma staining when jaundice is subsiding. Therefore, it may be concluded that the prin-

cipal cause of the yellow color of the organs must be the deposition of yellow substances in the tisssues, and that only a minor part can be caused by the yellow color of the circulating plasma.

Since bilirubin is firmly bound to a serum protein* that has properties similar to albumin, it was difficult initially to explain how bilirubin passed from the blood into the tissue fluid. The investigations of Drinker and co-workers[2] and Warren[15] resolved the problem. They demonstrated that tissue fluid always contains some protein. Stead and Warren found that under normal conditions the protein concentration of the tissue fluid of human skin is below .25%, but with rising venous pressure it may increase to approximately 1%; therefore, under normal conditions very little bound bilirubin could be present in the interstitial fluid. This low amount of bilirubin in the tissue fluid cannot in itself be the cause of the yellow color of jaundiced skin, but it is important as an intermediary link between the bilirubin of the serum and the bilirubin bound or deposited in the tissues.

A finding[17], common to all tissues which are more intensely colored in jaundice, is that they are very rich in elastin. It has also been found that elastic tissue has a great affinity for bilirubin *in vitro* as compared to cartilage, collagen and nerve tissue which stain very poorly with this pigment. This may account for the ready pigmentation of the skin, sclera, and blood vessels, which are rich in elastin, and its persistence in the skin after other body tissues have cleared. Distribution of these fibers probably accounts for the greater degree of pigmentation noted in the upper parts of the body, since Weidman[16] noted more elastic tissue cephalad than caudad.

As a consequence, it might be assumed that at least the greater part of the yellow color of the skin and mucous membranes in jaundice is caused by the elastin of the skin which binds the bilirubin (or its decomposition products) while the tissue fluid plays an insignificant role in this respect. In some way, the bilirubin bound to the trace of serum protein in the tissue fluid must be transferred to the elastin of the connective tissues in increasing jaundice, while the bilirubin must go the opposite way in subsiding jaundice.

That the binding of bilirubin or allied compounds by elastin is not the only factor contributing to the coloring of the skin is obvious when the case under discussion is considered. It is generally thought that the depigmented vitiliginous patches do not differ from normal skin in any respect except for a paucity or absence of melanoblasts. Accordingly, the elastic tissue content should be the same as in the surrounding integument, as indeed it was in special elastic tissue stains performed in our patient. Therefore, the absence of icteric pigmentation in the affected patches cannot be described on this basis.

If it is true that the depigmented patches in vitiligo show a paucity of capillaries and even those present are severely constricted[9], then it might be assumed that the achromic integument is not supplied with icteric plasma and, therefore, does not become pigmented. If this were true, there should be obvious temperature and nutritional differences between the chromic and achromic areas. [Some authors speak of such changes. See review by Rothman *et al.*[13].]

The discrepancy in the observed coloring of the skin may have been solely an optical one. This appears unlikely, since yellow should blend in more with flesh-colored skin rather than with white.

* The exact nature of the protein is not known, except that it has a high molecular weight and electrophoretically resembles albumin[7].

There have been other observations concerning the peculiar distribution of jaundice; however, these are not analogous to our case. Meakins[10] has commented on the absence of jaundice in edematous areas, provided the edema precedes the jaundice. He reported 6 cases in which circulatory failure and pronounced anasarca extending up approximately to the level of the nipples developed. Jaundice later developed in these, but the pigmentation did not appear in the skin over the areas where the edema was present. Meakins found, by direct analysis, that the edematous fluid did not contain pigment, whereas the plasma in the neighboring vein was laden with both free and bound bilirubin. Page[12] also described a curious phenomenon of unilateral jaundice in 2 patients who had cardiac failure and hemiplegia. Edema appeared only on the paralyzed side, whereas jaundice appeared on the other. It appears quite clear that bilirubin does not permeate the capillary wall in these cases. Why this should be so, is not fully understood, unless it is related to the increased hydrostatic pressure of the tissue fluids.

Summary. A case of vitiligo and jaundice has been presented. The observation was made that signs of icterus in the depigmented vitiliginous patches were not evident, although the surrounding skin was jaundiced. Similar observations have not been encountered and it is not possible to offer a satisfactory explanation for its occurrence.

REFERENCES

1. **Becker, S. W.,** and **Obermayer, M. E.:** Modern Dermatology and Syphilology, Philadelphia 1, J. B. Lippincott Company, 1940, p.1.
2. **Drinker, C. K.:** Ann. Rev. Physiol.,**7,** 389, 1945.
3. **Edwards, E. A.,** and **Duntley, S. Q.:** Am. J. Anat., **65,** 1, 1939.
4. **Jeghers, H.:** New Eng. J. Med., **231,** 88, 1944.
5. Idem: Personal communications.
6. **Laidlaw, G.:** Am. J. Med. Sci., **188,** 418, 1934.
7. **Lemberg, R.,** and **Legge, J. W.:** Hematin Compounds and Bile Pigments, Interscience Publishers, New York, 1949.
8. **Lerner, A. B.,** and **Fitzpatrick, T. B.:** Physiol. Rev., **30,** 81, 1950.
9. **Levy-Franckel, A., Guillaume, A. C.** and **Juster, E.:** Bull. Soc. Franc. de dermat. et. syph., **32,** 342, 1925.
10. **Meakins, J. C.:** J. Clin. Invest., **4,** 135, 1927.
11. **Ormsby, O. S.:** Diseases of the Skin, Philadelphia, Lea & Febiger, 6th Edition, 1943.
12. **Page, I. H.:** Am. J. Med. Sci., **177,** 273, 1929.
13. **Rothman, S., Rubin, L.,** and **Houston, M.:** Arch. Derm. and Syph., **48,** 400, 1943.
14. **Smith, L. W.,** and **Gault, E. S.:** Essentials of Pathology, Philadelphia, The Blakiston Company, p. 40.
15. **Stead, E. A.,** and **Warren, J. V.:** J. Clin. Invest., **23,** 283, 1944.
16. **Weidman, F. D.:** Arch. Dermat. and Syph., **24,** 954, 1931.
17. **With, T. K.:** Acta med. scand., **128,** 25, 1947.
18. Idem: Ibid. **122,** 501, 1945.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

GEORGE E. BURCH, M.D.
PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA
AND
C. THORPE RAY, M.D.
ASSOCIATE PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA
NEW ORLEANS, LOUISIANA

ACUTE SUPPURATIVE BRONCHOPNEUMONIA

By MORTON ZISKIND, M.D.
AND
MARIDEL SAUNDERS, M.D.

(From the Department of Medicine, Tulane University of Louisiana and Charity Hospital of Louisiana at New Orleans)

Historical Background. Acceptance of bronchopneumonia as a distinct disease entity was long fraught with difficulties. Laennec's[57] clinicopathologic correlation of the symptoms, physical signs, auscultatory characteristics and morbid anatomy of lobar pneumonia was immediately accepted by his contemporaries, but there was no such unanimity of opinion in regard to bronchopneumonia. To be sure, there was common agreement on many fundamental points: prevalence of this type of pneumonia in infants and the aged, its relationship to antecedent illness, notably grippe, measles and pertussis; its predilection for the posterior segments of the lung and the importance of prolonged decubitus in this localization; lack of correlation between its clinical manifestations and postmortem findings; and its unfavorable prognosis.

The main controversial points were: 1) the relationship, if any, between lobular pneumonia "capillary bronchitis", "suffocating catarrh", and frank, primary lobar pneumonia; 2) validity of carnification and hepatization of the lung as integral pathologic findings in pneumonia; 3) correct interpretation of the multiple pulmonary cavitations occasionally observed in lobular pneumonia, and the frequency of suppuration in pneumonic disease.

Berton[9], delaBerge[29] and Barrier[7] in France, and Seifert[95] in Germany were pioneers in establishing the integral relationship between bronchial inflammation and lobular pneumonia and in dispelling the notion, fostered even by such authorities as Barthez and Rilliet[86], that "the only anatomic difference between these diseases (lobular and lobar pneumonia) is a difference of extent".

In 1844, Legendre and Bailly[58], by insufflating the lungs of children dead of supposed pneumonia, were able to identify collapsed pulmonary tissue, to differentiate it from inflammatory infiltration, and so to clear up the confusion that had hitherto existed in regard to carnification (atelectasis) and true hepatization in extensive bronchopneumonia. At this same time, careful gross dissection and probing of the bronchial tree in both normal and pathologic specimens had led Barrier, Legendre and Bailly to conclude that the multiple, small, scattered cavities frequently found at autopsy in lobular pneumonia were, in fact, true abscesses, presumably formed by purulent dissolution of small bronchi and surrounding pulmonary tissue.

Following the discovery and identification, in the late nineteenth century, of the bacteria most commonly associated with bronchopneumonia, the next great advances were made during the influenza pandemic of 1918-19. The investigations of Opie, Blake, Small and Rivers[76], MacCallum[62], Chickering and Park[24], and other workers[21,40,112,113] defined the pathogenetic relationship between influenza and measles and the pneumonias which so frequently followed. Their descriptions of the pathologic characteristics of both suppurative and nonsuppurative bronchopneumonia are unsurpassed. Recent studies by Scadding[92] and Finland[34,114] have indicated that the secondary pneumonias associated with minor epidemics of influenza are practically identical with pandemic bronchopneumonia and are frequently suppurative. McNeil, Macgregor and Alexander[68] have found suppuration to be a fairly common occurrence (20%) in sporadic as well as epidemic bronchopneumonia of childhood.

In 1936-38 Scadding[91,93] called attention to the occurrence of chronic suppurative pneumonia, a progressive or recrudescent inflammation, characterized clinically by a protracted course, often resembling pulmonary tuberculosis, radiographically by shifting, spreading and resolving areas of consolidation, with or without cavitation, and pathologically by coexistent consolidation, resolution, organization and suppuration in different or the same areas of the lung. He pointed out the differences between chronic suppurative pneumonia on the one hand and delayed resolution of acute lobar pneumonia, fibrosis of the lung, and chronic interstitial pneumonia on the other.

In this country the Mount Sinai thoracic group[73,74,82,83,103,107] has led the way in defining the clinical, roentgenologic and pathologic characteristics of acute suppurative bronchopneumonia. The work of these men is largely responsible for growing awareness of this form of suppurative pulmonary disease, which has heretofore often gone unrecognized. Like other forms of bronchopneumonia, this disease usually follows a nonspecific upper respiratory tract infection. Pathologically, it is characterized by rather widespread involvement of several lobes which may progress to the point of clinically detectable consolidation. Suppurative lesions in the smaller bronchi may lead to obstruction with atelectasis or emphysema and to extensive peribronchial and interstitial inflammation, proceeding in some cases to necrosis. These changes are reflected clinically by the production of purulent sputum, and frequently by a protracted course, and radiographically by cavities, atelectasis, and focal emphysema. The mortality rate in the pre-antibiotic era was high, being determined principally by the

severity of the pulmonary involvement rather than by surgical complications, such as lung abscess and empyema. Now, however, early diagnosis is of more than academic interest, since prompt treatment can modify the course of the disease and prevent development of the chronic suppurative state described by Scadding.

Pathology. The anatomic changes present in bronchopneumonia have been a subject of interest to pathologists since the first half of the nineteenth century[7,9,29,60,80]. The opportunity to study the organs of patients who died of pneumonia during the epidemics of influenza and measles in 1918 led to the authoritative reports of Opie and his associates[76], MacCallum[62], Callender[21] and others[40,112,113]. The changes which occur in children in fatal sporadic cases have been precisely described and illustrated by McNeil, Macgregor and Alexander[68]. Excellent pathologic accounts have appeared in more recent literature[92,114], and good textbook descriptions are also available[35,52,63].

Though pathologic reports specifically devoted to suppurative bronchopneumonia are few, the cases in which suppuration predominated can be readily distinguished in the aforementioned large series. These postmortem descriptions necessarily deal with cases involving severe and extensive lesions. This is not a great obstacle to clinical interpretation, for the fundamental changes in the disease are alike in all cases. With the striking reduction in mortality rate resulting from the use of antibiotics, the lack of postmortem material makes us even more dependent upon the pathologic descriptions of the past.

Typically, the disease is diffuse and involves portions of several lobes. The dependent portions of the lungs are most frequently affected. Pulmonary zones drained by small bronchi, such as the lingula and middle lobe, are often involved. The extensiveness of the process and the frequent development of large areas of consolidation and atelectasis in children may be ascribed in large part to the small caliber of their bronchi. Generalized acute inflammation of the bronchial tree, extending down from the trachea, is usually present. The small bronchi are often dilated and contain pus, which can easily be expressed. Microscopic changes are most evident in smaller bronchi and terminal bronchioles; desquamation and necrosis of the bronchial epithelium are striking. Acute inflammatory infiltration of the bronchial wall is the rule and may lead to partial or total destruction of the involved bronchus.

After invasion of the bronchial wall, the infection enters the connective tissue planes of the pulmonary interstitium and involves the lymphatics and their associated lymph nodes. Suppurative lymphangitis is common, but it is unusual for the draining lymph nodes to break down. Inflammatory changes in the small arteries within the peribronchial septa may cause focal necrosis of associated pulmonary tissue. The infection spreads more or less concentrically from inflamed bronchi into surrounding tissue to form nodules of pneumonia. True lobular consolidations are relatively uncommon in this disease. Confluent zones of pneumonia occur frequently and, together with intervening areas of atelectasis, may grossly resemble consolidation. Within the nodules of pneumonia abscesses may develop as a result of purulent dissolution of the central bronchi and surrounding tissues. These cavities usually enlarge by the check-valve action of associated partial bronchial obstruction. Neighboring abscesses

may coalesce to form larger cavities, into which several bronchi open.

The widespread bronchial involvement also leads to numerous foci of atelectasis and emphysema. In the dependent portions of the lungs and in areas drained by bronchi of small caliber, especially in children, whole segments and lobes may be airless. Total collapse of a lung occurs only when large quantities of mucopurulent material are allowed to accumulate within the major bronchi. Focal emphysema depends upon partial bronchial obstruction by edema and secretions; the affected areas may swell to form pneumatoceles. At necropsy, it is common to see large zones of hyperinflated pulmonary tissue which do not collapse when the chest is opened[31]. Partial bronchial obstruction occasionally leads to alveolar rupture with bleb formation beneath the pleura or along the perivascular sheaths[65]. Such interstitial air is often associated with mediastinal and subcutaneous emphysema and spontaneous pneumothorax.

Pleural involvement is consequent to either rapidly extending interstitial inflammation or peripherally situated abscess. Sympathetic effusion, containing a predominance of neutrophiles, may be present alone or together with encapsulated empyema. Encapsulated empyema is generally consequent to perforation of an abscess into a zone bounded by preformed adhesions; in the absence of adhesions, rupture will result in total pyopneumothorax[74].

Predisposing Factors and Pathogenesis. Before considering the pathogenesis of acute suppurative bronchopneumonia, it seems worthwhile first to review briefly the mechanisms[4,88] which protect the lungs against the large numbers of airborne bacteria entering the respiratory tract several thousand times a day. These are, from above downwards, the nasal hairs acting as baffles to catch gross dust; nasopharyngeal secretions in which dust becomes mired; the epiglottis, which guards against aspiration of large particles; tracheobronchial secretions, which form an adhesive film to trap small particles and bacteria; the cilia, which continuously sweep small particles of all kinds up from the depths of the lungs toward the larynx; phagocytes, which engulf any solid matter breathed into the alveoli; and, finally, the cough reflex, which expels bodies too heavy to be propelled upward by ciliary action.

In health, these defenses are remarkably effective but not perfect. During sleep, material from the nose and mouth is aspirated into the tracheobronchial tree; it may, if large, viscous and heavily contaminated with virulent organisms, set up gangrenous inflammation in a healthy bronchus[106]. The protective mechanisms are also inadequate when the lungs are inundated by vomitus or by material aspirated through a tracheobronchial fistula. The position of the patient at the time he aspirates the material determines localization of the subsequent disease[14,16].

There is common agreement that acute bronchopneumonia, both suppurative and nonsuppurative, usually follows antecedent disease or some other condition which interferes with the cleansing mechanisms of the lungs. These factors may conveniently be considered as falling into two main groups: 1) those which more or less mechanically impair bronchial drainage and 2) those which attack the integrity of the bronchial membrane itself. Thus, stasis and bronchitis, plus a secondary infectious agent, are the elements concerned in the pathogenesis of bronchopneumonia.

Bronchial drainage will be impaired when pulmonary ventilation is depressed. In unconscious states, whether due to general anesthetics, excessive intake of drugs or alcohol, head injury or any other cause of coma, respiration is apt to be shallow; this situation is aggravated by inability of the patient to change position or cough. The respiratory excursions of postoperative and orthopedic patients are frequently limited by pain or fixed position. Patients with poliomyelitis and other neurologic lesions, as well as those with primary muscular weakness, are likewise unable to ventilate and cough effectively. Because of the small caliber of their bronchial tubes, infants and young children are particularly vulnerable to bronchial stasis. Patients with certain pulmonary diseases, such as bronchiectasis and emphysema, even though able to cough, cannot keep their bronchi free of secretions because of the anatomic distortions within the pulmonary drainage system. In chronic bronchitis swollen, boggy membranes and squamous metaplasia of the ciliated epithelium combine to prevent adequate drainage of the airways. In all these conditions, stagnant secretions provide a favorable medium for multiplication of bacteria inhaled or aspirated from the upper respiratory tract.

The integrity of the bronchial mucosa is subject to attack in a variety of ways. Acute upper respiratory infections may extend downward and set up acute bronchial inflammation. Bronchitis is an integral part of the pathologic picture of whooping cough and influenza and, most probably, measles[63] and scarlet fever[79] as well. Depending upon the severity of these primary infections, the bronchial tubes may be narrowed by inflammatory disease and the cilia may be immobilized by thick tenacious secretions, or the bronchial epithelium may actually be destroyed[1,66,102], leaving extensive denuded areas open to bacterial invasion. Acute bronchitis also follows inhalation of irritant gases; excessive secretions are poured out into the bronchial lumina, and if they cannot be removed, the stage is set for secondary infection.

The conditions which govern development of suppuration are not fully understood. That virulence of the invading organism is not the controlling factor is suggested by the ability of mild pathogens, such as *Streptococcus viridans*[74], to produce pulmonary suppuration. Resistance of the host is imponderable; however, experience in the fairly uniform population of Army camps during 1918-19 gave no indication that host resistance is an important factor. Failure of phagocytes to prevent local accumulation of rapidly multiplying bacteria may be responsible for suppuration[115].

Clinical Picture. The onset of suppurative bronchopneumonia is usually acute, with fever, chest pain and productive cough. Fever is typically moderate, between 100 and 102°, but occasionally attains high levels; it has no characteristic pattern. Chest pain appears early in most cases and is frequently so severe that the patient is compelled to suppress his cough. This may obscure, for a time, the one distinctive clinical feature of the disease: production of copious purulent sputum; in such cases, postural drainage is of value as a diagnostic, as well as a therapeutic, tool. Cough is variable in intensity, with a tendency to be paroxysmal. The patient rarely gives a history of wheezing or true chills, but chilly sensations are not uncommon.

Dyspnea is inconstant; it may be insignificant or the chief presenting complaint. It is most severe in those

patients with antecedent chronic bronchitis, massive pleural effusions, diffuse miliary involvement of the lungs, or extensive obstructive emphysema.

The most important information to be sought from the patient is an accurate description of his sputum, which is characteristically copious, purulent, and nonfetid early in the course of the disease. This history is often difficult to elicit, especially in cases seen late, since a mildly disagreeable sputum may be described by the patient as foul. However, if a definite statement concerning the presence or absence of fetid breath and sputum at onset of the illness can be obtained, it is of real value in ruling in or out putrefaction of the lung[106,110]. Blood streaking occurs at some time in at least 50% of cases, but a history of early severe hemoptysis casts doubt on the diagnosis of suppurative bronchopneumonia.

Physical examination reveals no characteristic signs. The usual findings observed in patients with uncomplicated bronchopneumonia are moderate tachypnea, bilateral medium coarse rales and rhonchi, and one or more small areas of dulness to percussion. In view of the frequency of chest pain, the rarity of pleural friction rubs is surprising. In some cases, the chest is entirely normal on examination, and it is the rule that physical findings are less than the involvement demonstrable roentgenographically.

Cyanosis is not typical but may be present in diffuse nodular infiltration or massive consolidation of the lungs. Although clubbing has been noted frequently by British authors (92% of Logan and Nicholson's cases[61]), it has not often been described in the cases reported in this country. In our series of 32 acute cases[116], clubbed fingers were encountered only once, in a patient with long-standing bronchiectasis.

General signs and symptoms are those usually associated with moderate to severe febrile illness: malaise, anorexia, occasionally headache, dehydration, and, in protracted cases, malnutrition and anemia. Significant toxemia is most apt to be found in the presence of total empyema.

Atypical Manifestations and Complications. *Complications Within the Lung.* The development of focal lung abscess is signalled by expectoration of pure pus and increased amounts of blood. If bronchial drainage of the abscess is impaired, chills, septic fever and increasing toxemia may ensue. In these cases of "shut-off" abscess[101], the danger of perforation into the pleural cavity or spill-over spread of infection, on sudden release of the obstruction, is increased.

In diffuse, small nodular involvement of the lung, multiple check-valve mechanisms in the small bronchi and bronchioles may cause an exceptional amount of obstructive emphysema. Here dyspnea and cyanosis are much more severe, and resolution is apt to be more rapid than in the usual case. Massive atelectasis of a lobe or an entire lung may supervene during the course of the disease and may give rise to sudden, acute dyspnea, cyanosis, vascular collapse and signs of mediastinal shift. Spread of the suppurative process to quiescent tuberculous foci may result in breakdown of a walled-off lesion, with appearance of tubercle bacilli in the sputum.

Finally, pulmonary embolism with infarction is a constant danger, the more so since suppurative pneumonia tends to run a protracted course, requiring prolonged bed rest. Sudden recurrence of chest pain, especially if accompanied by hemoptysis, in a patient who has been doing well suggests this complication.

Pleural Complications. With development of pleural complications, there may be recurrence of chest pain, fever and toxemia. Local signs and symptoms will depend upon whether the effusion is diffuse or encapsulated. Free fluid, in adequate amount, will manifest itself clinically by absolute dulness to percussion, faint or absent breath sounds, diminished tactile and vocal fremitus, and mediastinal shift. Cardiorespiratory function may be seriously embarrassed by massive effusion acting as a space-occupying lesion.

Definite physical signs of fluid will also be found over a large, peripheral loculated empyema, but interlobar empyema is not detectable on physical examination. The most serious complication of ruptured abscess is bronchopleural fistula with pyopneumothorax. The classical signs, succussion splash and bubbling respiration, are usually absent, and roentgenographic studies are necessary to make the diagnosis.

Other Complications. Direct extension of infection to the pericardium and mediastinum occurs in some cases. In others, metastatic infection of brain, meninges or other organs complicates the clinical picture.

Roentgenographic Signs. The roentgenographic changes associated with suppurative bronchopneumonia have been described in varying detail by different authors[79,82,83,98,103]. Rabin[83] has presented the most complete account and has closely correlated the findings on the Roentgen ray films with the pathologic changes. We shall draw heavily from his discussion. He states that the disease is characterized by the five following elements: (1) interstitial infiltrations, (2) lobular consolidation, (3) areas of atelectasis, (4) formation of cavities of varying sizes, (5) pleural complications.

In the less severe cases, the suppurative foci are minute and nodular, and streak-like infiltrations predominate. The atelectatic character of the process is indicated by the manner in which vascular markings are drawn together and by the presence of longer linear streaks. Complete resolution of the pneumonia may require several weeks; the last elements to disappear are the atelectatic zones.

Nodules and streaks are less prominent in the more severe form of the disease, for areas of lobular consolidation appear and often become confluent. These changes, which are most noticeable in children, may simulate true lobar consolidations but can usually be distinguished because signs of atelectasis are present. Large areas of atelectasis are detected by displacement of the fissures or mediastinal structures. Cavities are first noted within the consolidated pulmonary tissue. They are often multiple and may rapidly change in size. Many quickly disappear, but others develop tension and balloon out because of the valvular action of obstructing bronchial exudate. They may persist as thin-walled "air-cysts" or pneumatoceles after the surrounding densities have disappeared[2,20,27,77,78,83,100].

An unusual consequence of the inflammatory process is a solitary lung abscess. This lesion has a substantial wall. It may arise during the course of a diffuse process or develop within a relatively localized focus of the disease. The tendency of such abscesses to resolve has been emphasized[74] but has provoked some discussion[61,75,79]; some of them undoubtedly become chronic.

Evidence of pleural involvement is often present; free fluid is frequently seen in the pleural space and loculated collections are common. Encapsulated fluid usually has a parietal

representation but may be sealed within a fissure or between lung and diaphragm. Following perforation of a lung abscess, an intrapleural fluid level, indicating the presence of pyopneumothorax, is often present. The collection of air and pus may involve the entire pleural space but is more often encapsulated by inflammatory adhesions provoked by the antecedent abscess.

The disease within the lung, if sufficiently severe and of long duration, may lead to chronic inflammatory changes. Chronic lung abscess and persistent pneumatocele have already been mentioned. Permanent damage is most frequent in those areas which have poor drainage, the lingula and lower lobes; bronchiectasis and segmental or lobar contraction are most common in these areas[68].

Although suppurative bronchopneumonia is an important precursor of bronchiectasis[32,33], in most cases complete or almost complete resolution occurs. Even bronchiectases demonstrated by lipiodol have sometimes proved to be reversible[33]. The changes which remain on the Roentgen film in healed cases are of minor degree. Sets of vascular markings may still be drawn together, and linear scars may be detectable. In other instances some displacement of fissures and mediastinum may persist as the result of pulmonary scarring or overlying thickened pleura. Patients with normal films may exhibit moderate degrees of bronchial dilatation after lipiodol instillation.

Laboratory Findings. Hematologic findings in suppurative bronchopneumonia do not differ from those in other pneumonias[116]. Leukocytosis, usually between 12,000 and 20,000 white blood cells with neutrophilia, is to be expected in the majority of cases, but normal counts are found in about 20%[74]. Severe leukocytosis occurs in about another 20%. In protracted illness, anemia of moderate degree develops. Increased erythrocyte sedimentation rate is almost constant.

Results of sputum studies are inconclusive, with the notable exception that anaerobic bacteria play no part in this form of pulmonary suppuration. Neuhof and Thomas[74], whose accumulated experience is more extensive than that of all other reporters, point out the following reasons why they consider sputum cultures to be an unreliable diagnostic and prognostic guide in suppurative bronchopneumonia: 1) The correlation between nose and throat cultures and cultures of pleural fluid or pus from lung abscesses is poor. The former show mixed bacterial flora, whereas pure growth of a single pyogen is found in almost all of the latter. At times, the organism recovered from empyema or abscess pus is not present in the nasopharynx. 2) Repeated sputum cultures from the same patient show changes in nasopharyngeal flora. 3) There is little or no correlation between virulence of the organism and severity and course of the disease, since bacteria of low virulence, particularly *Streptococcus viridans*, have been found in pure culture in patients whose clinical course has differed in no way from that of patients with hemolytic streptococcal, staphylococcal or pneumococcal infections.

Other writers[61,75,79,93] have also reported that sputum cultures in this disease usually yield bacteria normally found in the human nasopharynx. Thus, acute suppurative bronchopneumonia occupies the somewhat anomalous position of a bacterial disease in which the causative organism seems to have little to do with the severity of the case. There are, however, two important exceptions to this general statement. First, in staphylococcal

pneumonia, whether epidemic or sporadic, this organism has, almost without exception, been found either in pure culture or in massive predominance in the sputum[39,64,85]. Since this is rarely the predominant organism in normal sputum, overwhelming numbers in the initial smear or culture of an untreated patient are strong evidence that the pneumonia is staphylococcal[85]. On the other hand, if the patient has received antibiotics or chemotherapeutic agents, staphylococcal preponderance in the sputum is of doubtful significance and may or may not mean superinfection[47].

Second, in times of epidemic influenza and measles, correlation between nasopharyngeal bacteria and bacteria causing secondary bronchopneumonia has been high. Experience in U. S. Army camps in 1918-19, when postinfluenzal pneumonia reached epidemic proportions, demonstrated that "effective control of streptococcus pneumonia will depend upon its recognition as soon as it appears, and bacteriologic examination of the sputum offers the readiest means for its identification"[76]. It was further demonstrated that the type of organism influenced to a great degree the type of pulmonary lesion; staphylococcal infections were associated with fulminating hemorrhagic pneumonia, streptococcal with a high incidence of empyema not found in other infections, and pneumococcal with lobar consolidations.

This disparity of opinion possibly arises from the fact that one group of observers studied postinfluenzal pneumonia, and the other studied sporadic cases. This would tend to support the contention of Neuhof and Thomas[74] that other factors are more important than bacteria in the clinical evolution of the disease.

With regard to the question of "mixed" versus "pure" infection, Neuhof and Thomas have reported pure cultures of one pyogen in empyema and abscess pus in cases with mixed sputum cultures. By contrast, it was the experience of Opie and his coworkers[76] that "mixed infection of the lung and even of the blood with pneumococci and hemolytic streptococci is often found, and study of the sputum during life has repeatedly shown that pneumococci alone are present shortly after the onset of the disease, whereas hemolytic streptococci appear late or are first discovered at autopsy. In such instances pneumococci have not frequently disappeared from the lung and at autopsy hemolytic streptococci alone are demonstrable." This was also the experience of the Empyema Commission[21].

In addition, "the staphylococcus has failed to invade the pleural cavity even when a pulmonary abscess has been present below the pleura, and in the only instance in which staphylococci have been isolated from the pleural cavity thoracotomy has been performed for empyema caused by hemolytic streptococci or an abscess communicates with both bronchus and pleura"[76]. Review of the cases reported by Reimann[85], Macgregor[64], Finland, Peterson and Strauss[34], and by Gibson and Belcher[39] tend, on the whole, to confirm the observations of Opie and his collaborators, with one important exception: in fulminating cases, pleural fluid contains staphylococci in the absence of lung abscess or pleural rupture. One may infer that the virulence of the organism does affect the clinical and pathologic picture. The extreme invasiveness of the staphylococci which causes fulminating pneumonia is presumably demonstrated by their ability to penetrate the intact pleura. Staphylococci of less virulence do not kill

the patient immediately, nor do they infect the pleura, but they are still able to destroy pulmonary tissue. Other organisms which, together with staphylococci, infect the lung might invade the pleura and be recovered in pure culture, which would not reflect the true state of affairs in the lung.

It may be concluded from this discussion that repeated sputum studies should be done for the following reasons: 1) Evidence is conflicting and further studies are needed before definitive conclusions about the importance of the type of pathogen can be reached. 2) In some cases, particularly staphylococcal infections, sputum studies have carried diagnostic weight. 3) Superinfections of the lung occur and are being reported with increasing frequency now that effective drugs are available to eliminate the primary pathogen[3,47,109]. If striking changes in bacteria coincide with deterioration in the condition of a patient receiving antibiotic therapy, and if the new organism is found to be resistant to that antibiotic, this constitutes strong presumptive evidence for a cause-and-effect relationship, and a change in therapeutic agent seems indicated.

Differential Diagnosis. Other diseases which produce pulmonary cavitation must be distinguished from suppurative bronchopneumonia. Since the roentgenographic appearance is not specific in these conditions, clinical and laboratory observations are the primary resources in diagnosis.

The presence of certain infectious agents can usually be determined by examination of the sputum. Acid-fast bacilli are invariably found when purulent material is expectorated from tuberculous cavities. The gross appearance of the sputum in Friedlander's pneumonia is often characteristic, and the bacilli are seen in great numbers on stained smears[36,44]. Pathogenic fungi, such as blastomycetes and actinomycetes, may sometimes be noted on direct smears, but cultures are usually necessary to determine the presence of these organisms and their nature. Since fungous infections are frequently systemic, the presence of distant lesions is a diagnostic clue. Material from the other involved sites is often available for smear, culture and biopsy.

Differentiation of suppurative bronchopneumonia from acute solitary aspiration abscess is not difficult[106]. There is no history of preceding upper respiratory infection; the source for the aspirated particle is usually found in necrotic fragments associated with diseased gums. The onset of symptoms is sudden, with early development of well localized chest pain. Foulness of the sputum is recognized as soon as the first purulent material is produced. As drainage improves, the offensive odor may disappear, but the patient and his intimates can readily recall when it was first noted. In patients in whom abscess is shut off from the bronchial tree, perforation into the pleura is common, and fetid pus is obtained by thoracentesis[101]. Once aspiration lung abscess has become chronic and has been complicated by spreads and spill-over infections, its manifestations and anatomic patterns are essentially the same as in chronic suppurative bronchopneumonia[61,75,97]. The nature of the original infection can then only be established by detailed information concerning the onset of the disease.

Abscess formation often occurs in diffusely infected pulmonary tissue distal to an obstructing bronchogenic carcinoma[15]. The presence of such a lesion may be suspected when there is continued collapse of the involved segment, lobe, or lung. In these cases persistent blood streaking is common and indicates the presence of an ulcera-

tive lesion; tumor cells are usually found in the bronchial secretions and sputum. Bronchoscopy and bronchography are of great value in demonstrating the tumor. If the obstruction lies within reach, adequate biopsy will reveal its nature. Other causes of bronchial narrowing, such as foreign bodies, perforating caseous and calcified lymph nodes and benign tumors, which may be associated with pulmonary suppuration, can be detected in this manner.

The peripheral nodular form of bronchogenic carcinoma may cavitate[15]. Though the sputum is purulent, absence of a history of acute bronchopneumonia and the thick irregular wall of the cavity on Roentgen ray film will suggest that the lesion is an ulcerating neoplasm. Frequently, the diagnosis of tumor is established by examination of the sputum. If the diagnosis is uncertain, exploratory thoracotomy should not be delayed in these cases.

Suppurative bronchopneumonia is generally easily distinguished from pulmonary infarction, which is also a common condition in postoperative and bedridden patients. In typical instances expectoration of blood without pus and the discovery of a source for emboli, usually in the legs, will establish the diagnosis of pulmonary infarction. Greater difficulty arises when infarction occurs to complicate suppurative bronchopneumonia. The presence of an embolic complication is practically assured if thrombophlebitis is found. If it is not discovered, a clear-cut picture of pulmonary embolism will be required for diagnosis, since hemoptysis and new areas of consolidation may also arise from erosion of vessels in abscess cavities and from spill-over spread of the pneumonic process.

Nomenclature. Bronchopneumonia is an excellent name for the disease the pathology of which has been outlined. The term links bronchitis to its associated pneumonia and differentiates it from pneumococcal lobar pneumonia. Since a variety of microörganisms produces anatomically identical bronchopneumonia, a bacteriologic classification is of value principally in epidemic periods and when special therapy is available for specific organisms.

Several authors feel that the term bronchopneumonia has been used loosely as a diagnostic wastebasket and should be superseded. Aspiration pneumonia, which has been suggested by Ramsay and Scadding[84], emphasizes the descending character of the infection but has a number of disadvantages. It does not differentiate the process from pneumococcal lobar pneumonia, which is also established by aspiration. The antecedent bronchitis and the interstitial reaction which are present are not suggested by the name. The changes ascribed to aspiration may be the result of accumulations of mucus secreted by the bronchial glands and not aspirated from above. Finally, in this country aspiration is commonly used to denote the pneumonia following putrid lung abscess and vomiting. Its use for still another entity would create confusion.

Other terminology has been offered but is subject to serious criticism. Atypical pneumonia, advanced by Cole[25a], only emphasizes divergence from the typical course of pneumococcal lobar pneumonia. It lacks any positive feature and would now be easily confused with primary atypical pneumonia. Pneumonitis has no clear clinical connotation. Coope[28] has listed the objections to its use: the term is a synonym for pneumonia and has no special anatomic or bacteriologic significance. Even when prefixed by "chronic," it throws no light on the nature of the disease process unless the specific clinical, anatomic and

bacteriologic antecedents can be established. Its indiscriminate use leads to great confusion concerning the pathogenesis of chronic lung abscess and bronchopneumonia as well as obstructive lesions in which spreads occur, either through unblocking or perforation across fissures.

The old term, bronchopneumonia, appears to have definite advantages over the names more recently proposed. Pathologic studies of experimental influenza emphasize the advisability of retaining a name for the secondary disease which implies that bronchitis determines the course of the infection.

Treatment. The key to effective therapy is prompt treatment before suppuration and necrosis have irreversibly damaged the lung[99]. It is, therefore, imperative to administer potent drugs in amounts sufficient to achieve a therapeutic level in the infected tissues early, while circulation to the area is still intact; once vascular thrombosis has occurred, the problem of producing adequate drug concentration is enormously increased. These considerations raise three important questions: 1) What drugs are effective? 2) Are larger doses of the appropriate drug required in these cases with extensive, inflamed, suppurating lesions than in other types of pneumonia? 3) What is the most effective route of administration?

Choice of Drugs and Size of Dose. The sulfonamides are generally ineffective in this disease. A few cures of staphylococcal pneumonia by sulfadiazine and sulfathiazole have been reported[13,34], but for the most part results have been so disappointing that some writers[74] question the advisability of using chemotherapy at all. The literature on antibiotic treatment of clear-cut cases of suppurative bronchopneumonia is scanty. There is abundant statistical proof that, except in infants[45], the mortality rate and complications of pneumonia as a group have been remarkably reduced by sulfonamides and antibiotics[51,70]. But much of this improvement is attributable to the beneficial effect of antibacterial drugs on pneumococcal lobar pneumonia, and it is not permissible to assume that the gratifying results achieved in an essentially benign disease will also ensue in destructive pulmonary lesions.

However, there is no doubt that adequate penicillin can greatly modify the course of suppurative bronchopneumonia and, at times, particularly in staphylococcal infections in children, effect dramatic cure[8,13]. Equally good results have been obtained in adults[8,12,39]. Streptococcal suppurative bronchopneumonia has likewise yielded to penicillin therapy; Kullman and Crellin[56] obtained complete healing in two patients with pulmonary cavitation in 24 and 36 days; 4 patients with empyema responded promptly to intrapleural and intramuscular penicillin. In our series[116], 2 patients with "mixed" infections were completely cured in 8 and 12 days; the first patient received gantrisin in addition to penicillin.

Even in those patients, and they are the majority, who do not respond so promptly, penicillin is beneficial. The mortality rate, which was 24% in the series of Neuhof and Thomas[74], is remarkably low; there were no deaths among Perry and Shapiro's[79] 6 patients who received this antibiotic. In our series[116], 28 of 32 patients were treated with penicillin; in 12, it was the only antibiotic used; 16 received other antibiotics, either in combination with penicillin or to replace it because it had proved ineffective. Two of our patients died; one was unresponsive to all forms of therapy; in the other it was possible to control suppuration

with penicillin alone, but the patient died of cor pulmonale resulting from long-standing bronchiectasis.

Penicillin also lowers the incidence of complications. Only one of our patients required operative intervention (for loculated empyema) during the acute stage of her illness; 5 others developed pleural effusions which responded to medical management. Except for one case of pleural effusion, which did not require surgical intervention, there were no complications in Perry and Shapiro's series[79]. In comparison with the serious complications reported by McNeil[68] in 120 children, of whom only 27 had suppurative pneumonia, complications during present-day treatment are minor; there were 34 cases of empyema, 10 of pericarditis, 8 of peritonitis, 4 of meningitis and one of pulmonary gangrene.

Spread of the destructive inflammatory process is limited by penicillin, and a high proportion of patients recover with no residual damage. Although recovery is slow, toxemia is virtually eliminated and the course of the illness is mild[39,79,116].

However, to avoid unwarranted optimism, it is well to keep several points in mind. Once the stage of chronic suppurative pneumonia has been reached, penicillin has little to offer beyond improving the patient's general condition and reducing the amount of his sputum, in preparation for pulmonary resection[61,75]. Second, penicillin-resistant bacteria are encountered with increasing frequency. Third, penicillin has a fairly narrow bacterial spectrum.

Fortunately, new antibiotics are available for use where penicillin fails. Of these, aureomycin has been the most widely used in suppurative bronchopneumonia. Collins, Gocke and Finland[26] have reported moderately good results in 20 cases of nontuberculous pulmonary suppuration. Fifteen of these patients were more than 50 years old, and almost all of them had chronic bronchopulmonary disease upon which an acute suppurative process had been implanted. Treatment with aureomycin effected improvement in the general condition and promptly reduced the quantity and purulence of the sputum in most patients. Though clearing of the lung proceeded slowly, surgical drainage of abscesses was necessary in only 2 patients. These observers were of the opinion that aureomycin was responsible for the benefits, since the patients had already received postural drainage, bronchoscopic aspiration, and penicillin when administration of aureomycin was begun.

Chandler, Schoenbach and Bryer[23] have reported complete cure of staphylococcal pneumonia in 2 infants. Leland and Allebach[59] have observed satisfactory response to aureomycin in 4 patients with staphylococcal pneumonia and one with nonspecific suppurative pneumonia. Aureomycin has also proved of value in the suppurative complications of mucoviscidosis[94]. Our own experience with aureomycin has been limited. In one patient, unresponsive to penicillin, aureomycin therapy resulted in prompt, complete cure. A second patient was cured more slowly, but completely. A third was left with residual pulmonary damage.

The value of terramycin in suppurative pneumonia must be seriously questioned. It is considered by some observers, among them Potterfield and Starkweather[81], to be more effective than penicillin in bronchopneumonias as a group. King and his associates[54] and Swift[104] have reported cures of suppurative cases, but the disastrous results published by Jackson and his colleagues[47] seem to us to cast doubt upon the advisability of terramycin therapy. Nine cases of severe staphy-

lococcal enteritis and 3 of staphylococcal pneumonia occurred among 68 patients with pneumococcal pneumonia; 4 of these 12 patients died. Four of the 23 patients with nonpneumococcal pneumonia also had severe staphylococcal enteritis; in a fifth patient severe bloody diarrhea developed, resulting in rectovesical fistula, uremia, acidosis and death. Altogether, 58% of the 91 patients suffered some toxic effects from terramycin. Further, Knight, Izler, and Meads[55] have reported terramycin failure in a patient who developed streptococcal empyema during treatment; this patient responded favorably to aureomycin therapy. In the 5 patients to whom we have administered terramycin, no serious side effects have been observed, and response was excellent in 2, fair in 2, and poor in one. However, in view of the fact that staphylococci are commonly found in cultures of sputum and lung in suppurative bronchopneumonia, even when they are not primarily responsible for the disease, it would seem unwise to employ a therapeutic agent which appears incapable of controlling them.

The use of chloramphenicol is, likewise, probably inadvisable. It has been reported effective in bacterial pneumonia but has no advantages over aureomycin and may lead to serious, even fatal, blood dyscrasia[30,41,108,111]. The literature on use of polymyxin, streptomycin and bacitracin in suppurative bronchopneumonia is too scanty to permit definitive conclusions.

It is clear that antibiotics are valuable in both early and late stages of suppurative bronchopneumonia. Even though rapid healing is not to be anticipated in the majority of cases, mortality rate, complications and morbidity of the disease are definitely diminished. In the present state of our knowledge, it seems best to institute treatment with penicillin in large doses, since it is effective against Gram-positive cocci, which are the most common etiologic agent, and is free from the unpleasant gastrointestinal side effects of aureomycin. However, one hazard of penicillin should be remembered: the possibility of superinfection with resistant organisms. Weinstein[109] and Appelbaum and Leff[3] have recorded such cases and recommended frequent bacteriologic studies during treatment.

If clinical response and diminution in extent of the pulmonary lesion are not satisfactory in 4 or 5 days, change to a broad-spectrum antibiotic is indicated. Aureomycin seems the best choice. Terramycin and chloramphenicol should be reserved for those cases resistant to other therapy.

The use of combined treatment in cases unresponsive to a single drug is still controversial. Penicillin-sulfonamide combinations have proved valuable[39], as has penicillin-streptomycin therapy[116]. But combinations of the new antibiotics have seemed in some instances to be less effective than either drug alone. Jawetz[48] has reviewed the question of antibiotic synergism and antagonism, which he first raised in 1950[49], and proposes a scheme of combined treatment based on theoretic considerations of the probable mechanism of synergism and antagonism. He suggests that antibiotics may be divided into 2 groups: 1) penicillin, streptomycin, bacitracin, neomycin; 2) aureomycin, chloramphenicol, and terramycin. Group 1 antibiotics are often synergistic, never antagonistic. Group 2 antibiotics have only a simple additive effect on one another but may be either antagonistic or synergistic to Group 1, depending upon the bacterium involved. *In vitro* evidence of the validity of Jawetz's hypothesis is good and should be kept in mind when

we contemplate piling on antibiotics in stubborn cases. Since 1950, we have used penicillin-streptomycin in cases when initial sputum smear and culture have shown Gram-negative bacilli in good numbers mixed with cocci. When change to a Group 2 antibiotic has been made, penicillin has been discontinued. As information on antibiotic synergism and antagonism accumulates, combined therapy is sure to become an extremely valuable weapon in handling refractory cases of pneumonia.

Size of Dose. Our ideas of adequate penicillin have undergone continued upward revision during the past 7 or 8 years. In 1945, Perry and Shapiro[79] achieved satisfactory results with 15,000 to 30,000 units of penicillin given intramuscularly every 3 hours. At present, 10 to 20 times that much is being ordered. The question of proper dosage in suppurative bronchopneumonia is particularly difficult to answer, since the bacteria in the sputum available for sensitivity tests are not necessarily the causative agents of the illness. In the absence of definite information, we recommend that dosage should err on the side of excess rather than on the side of possible inadequacy. In cases where sputum is copious and purulent, a presumptive diagnosis of suppurative pneumonia should be made, and a minimum of 200,000 units of aqueous penicillin should be injected intramuscularly every 3 hours. If satisfactory response is not observed within 48 hours, the dose should be doubled. If the doubled dose is still ineffective, a change to aureomycin is indicated.

Route of Administration. The standard route of administration of penicillin is by intravenous or intramuscular injection. However, during the past 8 years, the value of aerosol inhalation in chronic pulmonary suppuration has been clearly demonstrated by Bryson, Barach, Segal[18,19,96a,96b] and their associates and by many other observers. A more direct attack on the problem by intratracheal instillation of penicillin and other antibiotics has been attempted by May and Floyer[67], Kay and Meade[53], Rosenthal[89], and Metras[69]. This method of administration has also shown itself to be valuable in therapy of such conditions as chronic lung abscess, bronchiectasis, pulmonary cysts, and chronic bronchitis. The subject of parenteral, as compared with intratracheal or aerosol, therapy has recently been reviewed by Gaensler, Beakey, and Segal[37], who conclude that the latter routes of administration are most useful in chronic conditions, but should not alone be relied upon in acute pulmonary infections.

The use of these methods in acute suppurative bronchopneumonia has not received much attention, and results have been conflicting. Humphrey and Joules[46] obtained no response to penicillin inhalation in 4 patients with suppurative pneumonitis. Metras records complete clinical and roentgenographic healing in 17 of 29 patients with interstitial pulmonary suppuration after 4 to 8 intratracheal instillations of 100,000 units of penicillin at 2-day intervals. Clinical details of these 2 reports are not adequate to establish these cases definitely as acute suppurative bronchopneumonia. Segal and Ryder[96b] have expressed the opinion that, in streptococcal and staphylococcal pneumonia, penicillin inhalation is probably more effective than parenteral administration alone but suggest that combined aerosol and injection therapy is advisable in seriously ill patients. In suppurative pneumonia, in which, in addition to large or small areas of consolidated, airless lung, there is extensive plugging with infected atelectasis distal to the oc-

cluded bronchi, the ability of inhaled penicillin to penetrate bronchial pus in sufficient quantity to achieve a therapeutic level in the infected interstitial tissue seems questionable. The penicillin which does reach the systemic circulation is doubtless absorbed through healthy, uninvolved portions of the lungs[37]. The use of injections in these patients, is, therefore, recommended. In severely prostrated patients, in whom rapid absorption from intramuscular sites is doubtful, a priming dose should be given intravenously to assure an immediately adequate blood level.

Heathcote and Nassau[43] have recently described two penicillin esters, benzyl penicillin diethylaminoethyl ester hydriodide (LG1), and hydrochloride of benzylpenicillin diethylaminoethyl ester (LG2), which are readily diffusable from blood stream to sputum. Two hours after intramuscular injection of 1,000,000 units, the levels of LG1 and LG2 average 0.8 unit and 0.9 unit per cc. of sputum, as compared with 0.3 unit for sodium penicillin and less than 0.1 unit for procaine penicillin. In some cases, LG1 levels of 2.5 units at 2 hours and 1.5 units at 4 hours have been attained. The blood:sputum ratio of LG1 is 2:1, of LG2 1:1. Patients with bronchiectasis, pulmonary abscess and suppurative bronchopneumonia have shown definite clinical improvement during LG1 therapy with 50% to 60% reduction in daily sputum volume. We have had no experience with these penicillin esters, but on theoretic grounds they appear to be the drug of choice, since they overcome the inability of the older forms of penicillin to provide therapeutic levels throughout the infected areas.

Once suppuration is established and tissue destruction has occurred, the therapeutic problem is to induce and maintain adequate bronchial drainage. Postural drainage is indicated in the presence of cavities and in any case in which cough is nonproductive; when the patient is properly placed, according to the principles laid down by Nelson[72], it is remarkably effective. Obviously, accurate knowledge of the bronchopulmonary segments involved in the suppurative process is necessary for correct application of postural drainage[14]. The importance of multiple Roentgen views of the lungs in securing this essential information cannot be overemphasized. The patient should be encouraged to take deep breaths and force cough[5] during the exercise; when this is done, the drainage position, if uncomfortable, need not be maintained for more than a few minutes. Galloway[38] reminds us that the trachea slants anteroposteriorly in the chest, so that if postural drainage in the supine position is actually to be obtained, the foot of the bed must be elevated more than 6 inches.

Thick secretions and bronchospasm often interfere with effective cough. In such cases, expectorants, steam inhalations and bronchodilator drugs are of value[25]. If orally administered expectorants are ineffective, intravenous sodium iodide may be tried[4]. Trypsin has been administered as an aerosol for its mucolytic effect[60]. The patient may try to suppress cough if it is painful or may be too obtunded by his disease to make a tussive effort. Since suppression of cough must be prevented at all costs, mechanical irritation of the trachea may be necessary[22,42,71,90]. In case of trauma to the chest, intercostal neural block[90] offers a means of reducing pain to a point where the patient can be induced to cough. Inability to cough, whether from extreme debility, mental obtundation, or actual neuromuscular dis-

ease, constitutes indication for tracheotomy. In cases of massive atelectasis, if postural drainage and tracheal catheter suction fail, bronchoscopy must be done[71]. Patients with diffuse bronchial plugging with or without multiple foci of obstructive emphysema require oxygen.

Since the course of suppurative bronchopneumonia is frequently protracted, supportive treatment is a continuing concern. The patient loses body protein through suppuration; fever, anorexia and the metabolic disturbances attendant on prolonged bed rest increase nitrogen loss. Dehydration is often severe, particularly in dyspneic patients. Infection combines with these other debilitating factors to produce anemia. Bed sores may develop and set up a vicious circle of secondary infection, more fever, more protein loss, more bed sores. The necessity of good nursing care, high protein diet, adequate fluids and transfusions in these cases is obvious.

As a result of the efficacy of antibiotics and postural drainage, serious complications are becoming uncommon in suppurative bronchopneumonia, but mention should be made of the general principles of their treatment. The current trend is toward no operative intervention in acute aerobic solitary lung abscess, unless tension develops within the cavity and danger of perforation is imminent. Medical treatment of acute aerobic abscess is now attended with spectacular success. Christie, Aronovitch and Meakins[25] have recently reported their results in 8 patients treated with combined aerosol and intramuscular penicillin, postural drainage, forced cough, bronchodilators and expectorants. Six of their patients showed complete roentgenographic healing of the abscess cavity in from 15 to 40 days; healing was prolonged to 71 and 75 days in the 2 remaining patients but was also complete. Jewett and Dimond[50] report complete radiographic cure in 10 of 12 patients with acute lung abscess. One patient was left with residual bronchiectasis, and one patient died. If prompt, sustained response, as determined by serial roentgenograms, is not observed, early resection is indicated. In this connection, it is well to remember the admonition of D. T. Smith[99]: "the internist often gives inadequate treatment, and when the patient has made a partial recovery, prolongs the medical treatment to a point where the patient becomes a poor surgical risk."

Loculated empyema and empyema with bronchopleural fistula must be handled surgically. If no fistula is present, intrapleural instillation of penicillin[10,11,17,87], streptokinase and streptodornase[105], with repeated thoracenteses, may be tried; failure of prompt response necessitates open drainage to prevent chronicity. Simple pleural effusions are usually successfully managed by thoracentesis. Management of chronic complications of suppurative bronchopneumonia, such as fibrosis of the lung, bronchiectasis, chronic lung abscess, empyema, chronic bronchitis, is a discouraging problem. Where the condition is localized and amenable to surgical intervention, the patient may be restored to activity. But when the lungs are diffusely fibrotic, emphysematous and bronchiectatic, the physician has little to offer beyond symptomatic treatment; and antibiotics for the inevitable recurrent respiratory infections. The miserable condition of these chronic cases serves as a constant stimulus to treat acute respiratory infections with all the vigor at our command, in the hope of preventing such distressing sequelae.

Summary and Conclusions. 1) Acute suppurative bronchopneumonia is a

definite clinical entity with distinctive radiographic and pathologic features, which has not been widely recognized in the past.

2) It is a secondary bacterial disease superimposed upon certain viral diseases with or without upper respiratory tract infections. Careful management of the antecedent illness may prevent the development of secondary infection.

3) Untreated, suppurative pneumonia tends to run a protracted course and frequently leaves the patient with seriously incapacitating bronchial and pulmonary damage.

4) In the acute stage this disease will respond to prompt, vigorous treatment. Antibiotics, together with adjuvant therapy, of which postural drainage is the most important component, have been effective in most cases in reducing considerably the high mortality and high morbidity rates, the frequency of complications, and the extent of residual pulmonary damage in this destructive disease.

5) Any bacterial pneumonia which does not respond immediately to penicillin should be suspected of being suppurative in nature. Frequent roentgenograms of the lungs should be taken to detect promptly any evidence of pulmonary destruction or bronchial obstruction. If these are found, and if appropriate studies have excluded other specific cavitating infections, diagnosis may be considered established, and intensive treatment is mandatory.

REFERENCES

(1) **Adams, J. M., Pennoyer, M. D.,** and **Whiting, A. M.:** Am. J. Dis. Child., **1,** 162, 1946. (2) **Amberson, J. B.,** and **Spain, D. M.:** Trans. Assn. Am. Phys., **60,** 92, 1947. (3) **Appelbaum, E.,** and **Leff, W. A.:** J. Am. Med. Assn., **138,** 119, 1948.

(4) **Baker, J. M., Roettig, L. C.,** and **Curtis, G. M.:** Ann. Surg., **134,** 641, 1951. (5) **Barach, A. L.,** and **Bickerman, H. A.:** Bull. New York Acad. Med., **28,** 353, 1952. (6) **Barach, A. L., Silberstein, F. H., Oppenheimer, E. T., Hunter, T.,** and **Soroka, M.:** Ann. Int. Med., **22,** 485, 1945. (7) **Barrier, F.:** Traite Pratique des Maladies de l'Enfance, Paris, Fortin, Masson & Cie., 1842. (8) **Bennett, T. I.,** and **Parkes, T.:** Lancet, **1,** 305, 1944. (9) **Berton, E.:** Traite des Maladies des Enfants, Paris, Balliere & Cie., 1837. (10) **Blades, B., Hamilton, J. E.,** and **Dugan, D. J.:** Surgery, **17,** 572, 1945. (11) **Blades, B.:** J. Am. Med. Assn., **131,** 943, 1948. (12) **Blake, F. G.,** and **Craige, B., Jr.:** Yale J. Biol. & Med., **15,** 507, 1942-43. (13) **Blumenthal, S.,** and **Neuhof, H.:** Am. J. Dis. Child., **72,** 691, 1946. (14) **Brock, R. C.:** The Anatomy of the Bronchial Tree, London, Oxford Univ. Press, 1946. (15) Idem.: Guy's Hosp. Rep., **97,** 75, 1948. (16) **Brock, R. C., Hodgkiss, F.,** and **Jones, H. O.:** Ibid., **91,** 131, 1942. (17) **Brown, B., Ory, E. M., Meads, M.,** and **Finland, M.:** Ann. Int. Med., **24,** 343, 1946. (18) **Bryson, V.,** and **Grace, E. H.:** New Eng. J. Med., **237,** 683, 1947. (19) **Bryson, V., Sansome, E.,** and **Laskin, S.:** Science, **100,** 33, 1944.

(20) **Caffey, J.:** Am. J. Dis. Child., **60,** 586, 1940. (21) **Callender, G. R.:** "Pathology of the acute respiratory diseases", The Medical Department of the U. S. Army in the World War, Vol. II, pp. 1-570, Washington, D. C., Gov't. Printing Office, 1949. (22) **Cardon, L.:** J. Am. Med. Assn., **142,** 1039, 1950. (23) **Chandler, C. A., Schoenbach, E. B.,** and **Bryer, M. S.:** Pediatrics, **4,** 149, 1951. (24) **Chickering, H. T.,** and **Park, J. H.:** J. Am. Med. Assn., **72,** 617, 1919. (25) **Christie, H. E., Aronovitch, M.,** and **Meakins, J. F.:** Canad. Med. Assn. J., **62,** 478, 1950. (25a) **Cole, R. I.:** Acute Pulmonary Infections, DeLamar Lecture, 1927-28, quoted by Reimann[85], 1933. (26) **Collins, H. S., Gocke, T. M.,** and **Finland, M.:** Arch. Int. Med., **84,** 875, 1947. (27) **Conway, D. J.:** Arch. Dis. Child., **26,** 504, 1951. (28) **Coope, R.:** Thorax, **1,** 26, 1946.

(29) **de la Berge, L.:** J. Hebdom. des. Prog. des Sci., **2,** 414, 1834; **3,** 3, 41, 70, 1834.

(30) Editorial, J. Am. Med. Assn., **149,** 840, 1952. (31) **Ende, N.,** and **Ziskind, J.:** Surg. Gyn. & Obst., **94,** 57, 1952. (32) **Erb, I. H.:** Arch. Path., **15,** 357, 1933.

(33) **Field, C. E.:** Pediatrics, **4**, 231, 1949. **(34) Finland, M., Peterson, O. L.,** and **Strauss, E.:** Arch. Int. Med., **70**, 183, 1942. **(35) Forbus, W. D.:** Reaction to Injury, pp. 169-70, 387-92, Baltimore, Williams and Wilkins, 1943. **(36) Fremmel, F., Heunchsen, K. J.,** and **Sweany, H. C.:** Ann. Int. Med., **5**, 886, 1932.

(37) **Gaensler, E. A., Beakey, J. F.,** and **Segal, M. S.:** J. Thor. Surg., **18**, 546, 1949. **(38) Galloway, T. C.:** Arch. Otolaryng., **46**, 125, 1947. **(39) Gibson, M. O. J.,** and **Belcher, J. R.:** Quart. J. Med., **20**, 43, 1951. **(40) Goodpasture, E. W.:** Am. J. Med. Sci., **158**, 863, 1919.

(41) **Hargraves, M. M., Mills, S. D.,** and **Heck, F. J.:** J. Am. Med. Assn., **149**, 1293, 1952. **(42) Haight, C.:** Ann. Surg., **107**, 218, 1938. **(43) Heathcote, A. G. S.,** and **Nassau, E.:** Lancet, **1**, 1255, 1951. **(44) Heffron, R.:** Pneumonia; with Special Reference to Pneumococcus Lobar Pneumonia; New York, The Commonwealth Fund, 1939. **(45) Holzel, A.,** and **Wolman, B.:** Arch. Dis. Child., **25**, 282, 1950. **(46) Humphrey, J. H.,** and **Joules, H.:** Lancet, **2**, 221, 1946.

(47) **Jackson, G. G., Haight, T. H., Kass, E. H., Womack, C. R., Gocke, T. M.,** and **Finland, M.:** Ann. Int. Med., **35**, 1151, 1951. **(48) Jawetz, E.:** Arch. Int. Med., **90**, 301, 1952. **(49) Jawetz, E., Gunnison, J. B.,** and **Coleman, V. R.:** Science, **111**, 254, 1950. **(50) Jewett, J. S.,** and **Dimond, G. E.:** Dis. Chest, **18**, 478, 1950.

(51) **Kassowitz, K. E.,** and **Muscato, G. H.:** Dis. Chest, **21**, 161, 1952. **(52) Kaufman, E.:** Pathology for Students and Practitioners Vol. I, pp. 409-14. Philadelphia, Blakiston, 1929. **(53) Kay, E. B.,** and **Meade, R. H., Jr.:** J. Am. Med. Assn., **129**, 200, 1945. **(54) King, E. Q., Lewis, C. N., Welsh, H., Clark, E. A., Jr., Johnson, J. B., Lyons, J. B., Scott, R. B.,** and **Cornely, P. B.:** J. Am. Med. Assn., **143**, 1, 1950. **(55) Knight, V. H., Izler, H. L.,** and **Meads, M.:** N. Carolina Med. J., **11**, 679, 1950. **(56) Kullman, H. J. F.,** and **Crellin, J. A.:** Ann. Int. Med., **23**, 135, 1945.

(57) **Laennec, H. T. H.:** A Treatise on the Diseases of the Chest and on Mediate Percussion, (trans. by J. Forbes) New York, S. Woods & Sons, 1830. **(58) Legendre** and **Bailly:** Arch. Gen. de Med., **4**, 55, 184, 286, 1844. **(59) Leland, J. L.,** and **Allebach, N.:** New York State J. Med., **51**, 1159, 1951. **(60) Limber, C. R., Reiser, H. G., Roettig, L. C.,** and **Curtis, G. M.:** J. Am. Med. Assn., **159**, 816, 1952. **(61) Logan, A.,** and **Nicholson, H.:** Thorax, **4**, 125, 1949.

(62) **MacCallum, W. B.:** Pneumonia following Measles, Rockefeller Institute Report X, 1919. (63) Idem: A Textbook of Pathology, 7th Ed., pp. 500-501, Philadelphia, W. B. Saunders, 1940. **(64) Macgregor, A. R.:** Arch. Dis. Child., **11**, 195, 1936. **(65) Macklin, C. C.:** Arch. Int. Med., **64**, 913, 1939. **(66) Maxwell, E. S., Ward, T. G.,** and **Van Metre, T. E.:** J. Clin. Invest., **28**, 307, 1949. **(67) May, H. B.,** and **Floyer, M. A.:** Brit. Med. J., **1**, 907, 1945. **(68) McNeil, C., Macgregor, A. R.,** and **Alexander, A.:** Arch. Dis. Child., **4**, 12, 83, 111, 170, 270, 1929. **(69) Metras, H.,** and **Lieutier, J.:** Thorax, **2**, 196, 1947. **(70)** Metropolitan Life Ins. Co. Statistical Bulletin, Sept., 1948. **(71) Minor, B. R.:** Surg. Gyn. & Obst. Int. Abstr. Surg., **86**, 209, 1948.

(72) **Nelson, H. P.:** Brit. Med. J., **2**, 251, 1934. **(73) Neuhof, H.:** Pulmonary Abscess, Chapter 2, Vol. V, Lewis's Practice of Surgery, Hagerstown, Md., W. F. Prior and Co., 1949. **(74) Neuhof, H.,** and **Thomas, A.:** Arch. Int. Med., **75**, 45, 1945. **(75) Nicholson, H.:** Lancet, **2**, 549 and 605, 1950.

(76) **Opie, E. L., Blake, F. G., Small, J. C.,** and **Rivers, T. M.:** Epidemic Respiratory Disease; The Pneumonias and Other Infections of the Respiratory Tract accompanying Influenza and Measles, St. Louis, C. V. Mosby, 1921.

(77) **Peirce, C. B.:** Am. J. Roentgenol., **40**, 848, 1940. **(78) Peirce, C. B.,** and **Dirkse, P. R.:** Radiol., **28**, 651, 1937. **(79) Perry, S. P.,** and **Shapiro, R.:** Ibid., **50**, 351, 1948. **(80) Pfeiffer, B.:** Ztschr. f. Hyg., **13**, 357, 1893. **(81) Potterfield, T. G.,** and **Starkweather, G. A.:** J. Phila. Gen. Hosp., **2**, 6, 1951.

(82) **Rabin, C. B.:** J. Mt. Sinai Hosp., **8**, 32, 1942. **(83)** Idem: Radiology of the Chest, Golden's Diagnostic Roentgenology, Vol. I, Chapter 3, p. 1865, Baltimore, Williams & Wilkins Co., 1952. **(84) Ramsay, H.,** and **Scadding, J. G.:** Quart. J. Med., **8**, 79, 1939. **(85) Reimann, H. A.:** J. Am. Med. Assn., **101**, 514, 1933. **(86) Rilliet, F.,** and **Barthez, E.:** Traite Clinique et Pratique des Maladies des Enfants, Paris, Germier-Balliere, 1844. **(87) Roberts, J. E. H., Tubbs, O. S.,** and **Bates, M.:** Lancet, **1**, 39, 1945. **(88) Robertson, O. H.:** Ann. Int. Med., **18**, 1, 1943. **(89) Rosenthal, E.:** Lancet, **2**, 829, 1947.

(90) **Samson, P. C., and Burford, T. H.:** Bull. U. S. Army Med. Dept., **6**, 711, 1946. **(91) Scadding, J. G.:** Brit. J. Tuberc., **30**, 186, 1936. **(92)** Idem: Quart. J. Med., **6**, 425, 1937. **(93)** Idem: Proc. Roy. Soc. Med., **31**, 1259, 1938. **(94) Schwachman, H., Crocker, A. C., Foley, G. E., and Patterson, P. R.:** New Eng. J. Med., **241**, 185, 1951. **(95) Seifert, P.:** Die Bronchiopneumonie der Neugebornen and Sauglinge; eine nosologische-therapeutische Monologie, Berlin, G. Reimer, 1837. **(96a) Segal, M. S., and Ryder, C. M.:** New Eng. J. Med., **233**, 747, 1945. **(96b)** Iidem: Ibid.: **236**, 132, 1947. **(97) Sellors, T. H., Blair, L. G., Houghton, L. E., Thompson, V. C., and Pryce, D. M.:** Thorax, **1**, 146, 1946. **(98) Shanks, S. C., and Kerley, P.:** A Textbook of X-Ray Diagnosis, (Ed. 2) Vol. 2, p. 357, Philadelphia and London, W. B. Saunders, 1951. **(99) Smith, D. T.:** J. Thor. Surg., **17**, 72, 1948. **(100) Snow, W., and Cassasa, C. S. B.:** Am. J. Roentgenol., **37**, 217, 1937. **(101) Stats, D., and Neuhof, H.:** Arch. Int. Med., **76**, 154, 1945. **(102) Stuart-Harris, C. H., and Francis, C. H.:** J. Exp. Med., **68**, 789, 1938. **(103) Sussman, M. L.:** Am. J. Roentgenol., **40**, 22, 1938. **(104) Swift, P. N.:** Proc. Roy. Soc. Med., **44**, 1066, 1951.

(105) Tillet, W. S., Sherry, S., and Read, C. T.: J. Thor. Surg., **21**, 275 and 325, 1951. **(106) Touroff, A. S. W., and Moolten, S. E.:** Ibid., **4**, 558, 1935. **(107) Touroff, A. S. W., and Neuhof, H.:** Ibid., **10**, 618, 1941.

(108) Volini, I. F., Greenspan, I., Ehrlich, L., Gonner, J. A., Felsenfeld, O., and Schwartz, S. O.: J. Am. Med. Assn., **142**, 1333, 1950.

(109) Weinstein, L.: Am. J. Med. Sci., **214**, 56, 1947. **(110) Wessler, H.:** Abscess and Gangrene of the Lungs, p. 295, Diseases of the Respiratory Tract, Philadelphia, W. B. Saunders, 1936. **(111) Wilson, L. E., Harris, M. S., Henstell, H. H., Witherbee, O. O., and Kahn, J.:** J. Am. Med. Assn., **149**, 231, 1952. **(112) Winternitz, M. C., Wason, I. M., and McNamara, F. P.:** Pathology of Influenza, New Haven, Yale Univ. Press, 1920. **(113) Wolbach, S. B.:** Bull. Johns Hopkins Hosp., **30**, 104, 1919. **(114) Wolleman, O. J., and Finland, M.:** Am. J. Path., **19**, 23, 1943. **(115) Wood, W. B., Jr., and Smith, M. R.:** J. Exp. Med., **92**, 85, 1950.

(116) Ziskind, M. M., and Saunders, M.: Unpublished data.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.
CLINICAL PROFESSOR OF PSYCHIATRY, UNIVERSITY OF COLORADO SCHOOL OF MEDICINE

AND

PHILIP R. A. MAY, M.D.
ASSISTANT CLINICAL PROFESSOR OF PSYCHIATRY,
UNIVERSITY OF COLORADO SCHOOL OF MEDICINE
DENVER, COLORADO

SOME RECENT CONTRIBUTIONS IN THE FIELD OF GERIATRIC PSYCHIATRY

By ALBERT J. SILVERMAN, M.D.

(From the Department of Psychiatry, University of Colorado School of Medicine, Denver, Colorado)

UNTIL recently, the medical profession stood accused of a great failing; that is, lack of interest in the problems of the aged. As late as 1950, Bowman[7], in reviewing the progress of geriatric research, had to state, "—nothing very new or startling—". In the past few years, physicians interested in this problem, were at last able to see the beginning fruits of their campaign to bring to the attention of their colleagues the plight of our elders.

The wave of articles and statistics indicating the scope of the problem and the necessity of its active solution has resulted in more and more interest. Specialists in the various fields of biochemistry, internal medicine, surgery, psychiatry and others have begun to do active work in geriatrics, appreciating its research potential.

Geriatric literature has, by this time, become voluminous. Two widely read journals and two societies interested in problems of the aged have been organized. The recent increased pace of scientific investigation results in the need for periodic compilation of literature dealing with this topic. This article will attempt, therefore, to review some of the most recent publications dealing with the psychiatric aspects of geriatrics.

Attention may first profitably be directed to the comprehensive review of this subject by Frank[19]. In addition, Sands[38] has recently published an excellent survey of neurologic and psychiatric disorders in the aged, concluding with brief but pertinent remarks about treatment. Management of the elderly mental patient is also reviewed by Gardner[22] in a recent article.

Interest of the medical profession has been paralleled by interest and effort on the part of government agencies. More and more accounts are noted in our newspapers, dealing with the formation of commissions for the study of the problems of the Aged[33]. Many states[14] have already set up divisions of adult health in their public health departments. The laity is starting to demand and has received lecture series in mental hygiene. These have included "talks on growing old" by physicians, such as that given by Ebaugh[15] who stated, "—not only to add years to life, but more important to add life to years."

In discussing the existence of a negative attitude toward the elderly, Ginz-

berg[23] states that this is due to the conviction that old people are lost causes. He believes this attitude is present in most cultures, although frequently camouflaged by excessive filial piety. To pave the way for better social and personal adjustment of the elderly, this author indicates that physicians must understand these inner feelings that exist in the populace.

The above-mentioned negative attitude is of course seen in the retirement policies of many industries. Ficarra[17] deplores this tendency to retire people at fixed and specific ages. He has coined the term "mental euthanasia" to describe the result of this policy which destroys the productivity of an individual without taking into account his particular potential. Would we doctors appreciate the prospect of forced retirement at age 65?

EMOTIONAL FACTORS AND PSYCHOTHERAPY. Organic disease in the brain, although important, is no longer considered the only factor in the development of senile or arteriosclerotic psychoses. Emotional factors are now thought to play an important role. Brain damage is as frequent in nonpsychotic as in psychotic oldsters. The psychosis is regarded as the result of the interaction of organic and functional factors. Aging people are thus less likely to develop functional or "organic" mental illness if they have healthy personalities, feel secure, are wanted, and can engage in useful activity which stimulates the preservation of their personality organization.

Boyd and Braceland[8] hence urge the general practitioner not to despair at the management of the problems of the aged. Aged patients with emotional or organic illness, unless very far advanced, may be helped by maintaining in one's patients a feeling of emotional security and a sense of dignity. A secondary objective is the interpretation to relatives responsible for their care, of the nature of the problem, so as to gain their assistance. The combination of judicious medical and psychiatric treatment may achieve gratifying results.

Laycock's statements[29], as to the nature of the needs of old people, apply of course to all of us, and are repeated here because of their universality: 1.) Need for affection. 2.) Need for the feeling of belonging. 3.) Need for independence. 4.) Need for achievement. 5.) Need for recognition and approval. 6.) Need for a feeling of self-esteem.

Thus, according to Clow[11] and Allen[1], concentration on emotional factors, such as the patients' need for responsibility and desire to get well, may often result in amazing success in spite of the presence of brain lesions.

Himler and others[27,2] stress that commitment of old people should be a last resort, utilized only if medical and psychiatric treatments in the home or general hospital have failed. Levy[30] and Cook[12], reviewing the problem of overcrowding in our mental hospitals, suggest that multiple small active-treatment homes or hospitals would alleviate some of the pressure. Active treatment would enable more patients to return to society, thus resulting in a fewer number of cases requiring custodial care.

It has been noted above that emotional factors are now thought to play an important role in the genesis of organic psychoses. In addition to this, it has also been recently brought to our attention that actually, functional disturbances are much more frequent in the aged than organic dementias [31,42,37]. Depression is the most frequent clinical syndrome seen, and in most cases is quite amenable to appropriate therapy.

Alvarez[3] has stressed the tendency for depressed patients to present themselves to the practitioner with multiple

somatic complaints, which will only subside under psychiatric treatment. Stern and his co-workers[41], studying a group of patients in their old age counselling service, observed that bereavement was a frequent occurrence in their patients. They also reported that somatic illness appeared to be accentuated or precipitated by the bereavement. These patients were treated by environmental manipulation and by exploiting all available channels of sublimation.

In summarizing the factors necessary for a happy adjustment in old age, Blake[6] suggests that oldsters do best when they have hard work to do over long periods of time, when they have a few important social activities, and when their lives are relatively well organized and oriented around religion.

Psychotherapy in the aged[13,24,43] aims at the recognition by patient and doctor of the patient's reduced resources, and a fuller utilization of remaining resources resulting in a healthier adaptation. Until recently, most therapists felt that elderly people were not "flexible" enough to undergo the difficulties of formal psychotherapy. It has now become relatively common practice among reliable psychoanalysts to attempt to help patients in their 50's, 60's and 70's.

SOMATIC TREATMENT. Prout and Hamilton[35] report on the results of electroshock therapy in elderly patients. This in their hands was successful in helping cases of affect disturbances primarily, such as depressive psychosis. They have noted that medical attention to exhaustion, toxic and nutritional factors, as well as occupational and psychotherapy, have often obviated the necessity for electro-shock therapy. When electro-shock seemed advisable, the cardiovascular status of the patient was observed carefully, the treatment being considered only if the patient was able to walk 100 yards without distress. Curare was used routinely with good results, appearing to lessen the strain on the aged and often brittle skeletal system, and on the cardiovascular state.

Pituitary gonadotropin appeared to be useful in the treatment of some cases of male senility[25]. It was found to be less toxic than testosterone, and often resulted in a degree of euphoria, restoring the patient's mental and physical sense of well-being.

Caldwell and Watson[10] studied the effects of estrogen and progesterone on 30 elderly women. Psychological tests were administered before and after the treatments, which consisted of giving the above drugs in dosages that would cause a recurrence of cyclic bleeding in these post-menopausal patients. The findings of these investigators suggest that after a course of hormone therapy many of the patients seemed to show more willingness to expend intellectual energy, hence showing some improvement in their ability to learn.

Nicotinic acid or its amide has now been used for many years in attempts to improve the cerebral circulation. Moore and co-workers[32] report that alternating injections of nicotinic acid and intravenous histamine proves to be a much more effective dilator of cerebral blood vessels. Using this technique in 24 patients with cerebral arteriosclerosis, they noted decided improvement in 23 of them.

Some investigators[4,28] have determined that arteriosclerotic psychoses may be benefited by thyroid hormone-vitamin B-complex therapy. Early cases are reported to be especially amenable to this form of therapy, although even advanced cases have shown improvement. This treatment has also resulted in a reduction of blood pressure in some cases of hypertension.

RECENT RESEARCH. Investigation has been very active along many different

lines, but lack of space will only permit discussion of a few ideas. Shock's work[40] has indicated that one of the characteristics of aging is that more time is required by the aged individual to adjust to physiological stress. Homeostatic mechanisms are more sluggish. The adaptability of the aging person to psychological stress, is hence, by inference, also slower. Granick[26] supports this contention when he records that recovery from emotional disturbances in the aged is not as fast as in younger people. Granick has also noted that in the period over the age of 65 there is an increased incidence of emotional disorders. In the cases studied by him the most obvious precipitating factor was insecurity. The work of Riemer[36] seems to support this idea. Studying chronic schizophrenics, this author found that the incidence of senile psychoses in chronically hospitalized schizophrenics was negligible. However, schizophrenics who adjusted somewhat better and were able to leave the hospital, seemed much more prone to develop senile psychotic states. The recovered schizophrenic is an individual who is making a tenuous adjustment to the many stresses of reality, and thus he tends to succumb relatively easily to his decreasing neural resources. The hospitalized schizophrenic, on the other hand, remains protected, and is spared the responsibility of coping with the many problems of the aging individual in society. Thus, Riemer's investigations tend to support very strongly the concept that emotional factors are very important in the development of a senile psychosis.

Working with a community group of elderly people, Busse, Barnes, and Silverman[9] studied some aspects of adjustment in oldsters. They noted a shift in religious feeling which included, contrary to opinion and expectation, a less strict adherence to religious dogma. Sexual desires and activity persisted in about 50% of the group. Lack of sexual outlets appeared to be an important anxiety producing factor. This was noted to be present to a greater extent in the women of the group. (Schuster's careful study[39] of a 106-year old man is of interest in this connection. Schuster's patient feared impotence because it seemed to mean that his body was beginning to fail him!)

The above authors[5], recording electroencephalograms on the same community group, noted a high incidence of diffuse slow waves, and a 37% incidence of temporal lobe focal disturbances. These findings appear to support the evidence that all of us, as we get older develop some brain change, and that other factors must operate to result in clinical disease. Frost[21], in correlating psychological tests with these findings, was able to show that the group with diffuse electroencephalographic abnormalities appeared to have significant decreases in the clarity of their perceptions. Temporal lobe focal damage did not appear to affect perceptual clarity to the same extent.

Obrist[34], also recording the electroencephalograms of clinically well elderly subjects, was able to show that there was a higher percentage of diffuse abnormalities in the group over 80 years than in the group 65 to 79 years.

Cerebral anoxia has long been known to be a factor in some organic psychoses. Freyhan[20] and Fazekas[16], using the nitrous oxide technique, report that there is a decrease in cerebral blood flow, a decrease in oxygen used, and an increase in cerebral blood vessel resistance in cases of senile and arteriosclerotic psychoses. There was no noteworthy difference in the readings obtained in these two clinical entities. In addition it might be well to point out that elderly non-psychotic people also revealed a relative cerebral anoxia, and

that no correlation could be made between readings obtained and mental symptomatology.

Finally, it may be of interest to repeat the finding of Fisher[18]. This author reports that unilateral or bilateral internal carotid occlusion is often a major factor in the development of the above-noted reduced cerebral blood flow and anoxia. The importance of this finding is apparent. Once this diagnosis is established, surgical anastamosis of the patent portions of the artery may at times be feasible.

Thus the work goes on. The second half of this century is indeed becoming the age of geriatrics. Once hustled into a state mental institution, the elderly person who develops mental symptoms is now being given a second look.

More and more of our older patients are being treated at home and in general hospitals. The diagnosis of senile dementia should not be, and no longer is a one-way ticket to the nearest state hospital. Undue pessimism has now given way to optimistic investigation and help. Many of these cases have proven not to be incurable at all and have, after treatment, returned to the community to enjoy their admittedly lessened resources to the fullest.

REFERENCES

(1) **Allen, E. B.**: New Eng. J. Med., **245**, 677, 1951. (2) **Allen, E. B., and Clow, H. E.**: Geriatrics, **7**, 117, 1952. (3) **Alvarez, W. C.**: Geriatrics, **7**, 295, 1952.

(4) **Bamford, T. E.**: New York State J. Med., **51**, 2913, 1951. (5) **Barnes, R. H., Busse, E. W.,** and **Silverman, A. J.**: Paper read at semi-annual meeting of the Central Electroencephalographic Society, Madison, Wis., Oct. 18-20, 1952. (6) **Blake W. D.**: Paper read at annual meetings of the Gerontological Society, Washington, D. C., Sept. 5-7, 1952. (7) **Bowman, K. M.**: Am. J. Psychiat., **106**, 524, 1950. (8) **Boyd, D. A.,** and **Braceland, F. J.**: Med. Clin. N. Am., **34**, 1091, 1950. (9) **Busse, E. W., Barnes, R. H.,** and **Silverman, A. J.**: Paper read at annual meeting of the Gerontological Society Inc., Washington, D. C., Sept. 5-7, 1952.

(10) **Caldwell, B. M.,** and **Watson, R. I.**: J. Gerontology, **7**, 228, 1952. (11) **Clow, H. E.**: Mental Sci., **34**, 592, 1950. (12) **Cook, L. C., Cunningham, D. E.,** and **Maclay, W. S.**: Lancet, **1**, 377, 1952. (13) **Cutner, M.**: Brit. J. Med. Psychology, **23**, 75, 1950.

(14) **Desmond, T. C.**: Report of the New York State Joint Legislative Committee on Problems of the Aging, Albany, N. Y. 1952.

(15) **Ebaugh, F. G.**: Paper read at Lecture Series, Mental Health, Denver, Colorado, April 9, 1951.

(16) **Fazekas, J. F., Alman, R. W.,** and **Bessman, A. N.**: Am. J. Med. Sci., **233**, 245, 1952. (17) **Ficarra, B. J.**: Geriatrics, **7**, 62, 1952. (18) **Fisher, M.**: Canad. Med. Assn., J., **65**, 1, 1951. (19) **Frank, J. A.**: Am. J. Med. Sci., **222**, 109, 1951. (20) **Freyhan, F. A., Woodward, R. B.,** and **Kety, S. S.**: J. Nerv. & Ment. Dis., **113**, 449, 1951. (21) **Frost, L. L., Thaler, M. B., Busse, E. W.,** and **Shy, M. G.**: Paper read at annual meeting of the Gerontological Society, Inc., Washington, D. C., Sept. 5-7, 1952.

(22) **Gardner, W. P.**: Minn. Med., **33**, 353, 1950. (23) **Ginzberg, R.**: Geriatrics, **7**, 297, 1952. (24) **Goldfarb, A. I.**: Paper read at annual meeting of the Gerontological Society Inc., Washington, D. C., Sept. 5-7, 1952. (25) **Gould, W. G.,** and **Strosberg, I.**: Med. Times, **79**, 622, 1951. (26) **Granick, S.**: J. Gerontology, **5**, 361, 1950.

(27) **Himler, L. E.**: J. Am. Med. Assn., **147**, 1330, 1951.

(28) **Israel, M., Freed, I., and McLeod, A. J.**: Med. Record, **162**, 14, 1949.

(29) **Laycock, S. R.**: J. Canad. Med. Assn., **63**, 111, 1945. (30) **Levy, S.,** and **Southcombe, R. H.**: Northwest Med., **50**, 501, 1951.

(31) **Madden, J. J., Luhan, J. A., Kaplan, L. A.,** and **Reidy, J. J.**: Illinois Med. J., **100**, 129, 1951. (32) **Moore, D. E., Morris, C. W., Smith, F. V.,** and **Lawson, J. L.**: J. Clin. Psychopath., **12**, 249, 1951. (33) **Mountin, J. W.**: Public Health Reports, **65**, 795, 1950.

(34) **Obrist, W. D.**: Paper read at annual meeting of the Gerontology Society Inc., Washington, D. C., Sept. 5-7, 1952.
(35) **Prout, C. T.**, and **Hamilton, D. M.**: Bull. New York Acad. Med., **28**, 454, 1952.
(36) **Riemer, M. D.**: Psychiat. Quart., **24**, 309, 1950. (37) **Roth, M.**, and **Morrissey, J. D.**: J. Mental Sci., **98**, 66, 1952.
(38) **Sands, I. J.**: New York State J. Med., **51**, 2370, 1951. (39) **Schuster, D. B.**: Am. J. Psychiat., **109**, 112, 1952. (40) **Shock, N. W.**: Geriatrics, **7**, 248, 1952. (41) **Stern, K., Williams, G. M.**, and **Prados, M.**: Am. J. Psychiat., **108**, 289, 1951.
(42) **Tilkin, L.**: Geriatrics, **7**, 56, 1952.
(43) **Wayne, G. J.**: Ann. West. Med. & Surg., **6**, 88, 1952.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. RICHARD A. KERN, Temple University School of Medicine, Philadelphia 40, Pa. Articles are accepted for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

MANUSCRIPTS should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. ILLUSTRATIONS accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. The recommendations of the American Medical Association Style Book should be followed. REFERENCES should be numbered and at the end of the articles arranged alphabetically according to the name of the first author and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers).

RETURN POSTAGE should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

100 REPRINTS will be supplied gratis. Covers will be omitted on all articles. Orders of additional reprints will be supplied in multiples of 100.

PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF OCTOBER 21, 1952

A Simple Method of Both Seeing and Recording the Direct Body Ballistocardiogram Through the Ordinary Compound Microscope, Giving a Record Easily Standardized. C. B. HENDERSON, M.D., and E. W. BIXBY, M.D. (Department of Therapeutic Research, University of Pennsylvania). Ballistocardiograms taken directly from the body by a bar across the shins (the Dock method) can be readily both observed and recorded through the ordinary compound microscope. When a rigid stylus is attached to the bar across the shins of a patient lying on a rigid table, and this stylus is observed with the low power of a microscope resting on the table, the ballistic movements are readily seen and their overall magnitude can be easily measured with a micrometer in the eyepiece; although the individual waves occur too rapidly to permit detection of their size or contour. By means of a photokymograph this ballistocardiogram can be readily recorded. The resulting record seems identical with that recorded by a photoelectric cell (the Sanborn direct displacement ballistocardiogram) but has the great advantage of being more readily standardized. In this microscope method a steady force applied to the body of the subject in the footward direction produces a permanent and readily measured displacement of the record base line; while in the electrical methods a similar continuing force produces only a small and transitory effect, which cannot be used successfully for standardization.

Effects of Electroshock upon the Cerebrospinal Fluid of Dogs. M. SPIEGEL-ADOLF, M.D., C. W. UMLAUF, M.D., and E. G. SZEKELY, V.M.D. (From the Departments of Colloid Chemistry and Experimental Neurology, Temple University.) Former studies of spectrophotometric changes in the cerebrospinal fluid (CSF) (J. Neuropath. & Exper. Neurol., **4**: 277, 1945, Am. J. Psychiat., **104**: 697, 1948) following electrically induced convulsions in dogs and humans were extended; especially the influence of the kind of current used was studied. The spectrophotometric results were analyzed by chemical determinations of CSF constituents similarly as in previous studies of various diseases (J. Nerv. & Ment. Dis., **113**: 529, 1951). Twenty-two dogs were tapped before and after a series of 6 electroconvulsions; in 12 dogs sinusoidal current, in 10 brief rectangular pulses were used. The CSFs were studied ultra-spectrographically over a range from 220 to 310 mμ; the ascorbic acid content was determined simultaneously according to Robinson and Stotz, the protein was measured electrocolorimetrically by the sulfosalicylic acid method. A comparison of these data shows only in the CSF of dogs stimulated by sinusoidal current an increase in the extinction coefficient. The corresponding ascorbic acid and protein values are practically unchanged, nor are significant changes detected in the dogs stimulated with rectangular pulses. If the analytic ascorbic acid and protein values are converted into extinction coefficients and deducted from the extinction of the whole CSF, then the difference D in the dogs treated with sinusoidal current shows a statistically significant increase, in agreement with our former observations in humans and in dogs. Our results are furthermore a proof

that the increase in optical absorption is not due to an increase of ascorbic acid or protein. They may be due to the presence of nucleic acids, or of derivatives liberated by a transitory damage of the cells of the central nervous system, or both. This damage is apparently not caused by the convulsions but probably due to the higher heating power of the sinusoidal current compared with that of the rectangular pulses applied.

The Effect of Low Oxygen Upon the Resistance to Pulmonary Blood Flow. R. C. STROUD, PH.D., and H. RAHN, PH.D., (Departments of Physiology and Pharmacology, University of Pennsylvania Graduate School of Medicine, Philadelphia, and Departments of Physiology and Vital Economics, University of Rochester School of Medicine and Dentistry, Rochester, N. Y.). Pulmonary resistance was calculated as the pressure drop between the pulmonary artery and vein divided by the rate of blood flow. Measurements were obtained on nembutalized (28 mg./Kg.) dogs with catheters in the main pulmonary artery and vein. Pressures were determined by means of saline manometers. Blood flow was measured by the Fick method. Following control determinations while breathing room air, each dog breathed one or more of the test gas mixtures. For 22 dogs, the calculated resistance increased 25 and 48%, respectively, breathing 8 and 15% O_2, and decreased 11% with 30% O_2. Five dogs breathing 5% CO_2, 25% O_2, 70% N_2 showed no significant resistance change. In no case was the pulmonary venous pressure changed significantly by the breathing of a test gas mixture. Three of the dogs which showed an increased resistance while breathing low oxygen were sympathectomized from the middle cervical ganglia through T-9. Three weeks after the operation all failed to show an increase in resistance with low oxygen. The rather large quantitative variability observed may be due to the depth of anesthesia. In unanesthetized dogs with indwelling tubes in the pulmonary artery it was found that the pulmonary arterial pressure increased about 100% when 8% oxygen was breathed. One of these dogs had previously failed to show any response under nembutal anesthesia. Reasons are presented for interpreting the observed resistance increases as representing constriction of pulmonary blood vessels.

BOOK REVIEWS AND NOTICES

MODERN ELECTROCARDIOGRAPHY. VOLUME 1. THE P-Q-R-S-T-U COMPLEX. By EUGENE LEPESCHKIN, M.D., Assistant Professor of Experimental Medicine, University of Vermont College of Medicine. Pp. 598; 91 ills. Baltimore: The Williams & Wilkins Co., 1951. Price, $12.00.

THE purpose of this book is to provide a comprehensive but concise summary of the progress of electrocardiography since 1933, when the publications of F. N. Wilson and his school introduced multiple precordial leads and initiated a new era of scientific thinking in this formerly largely empirical discipline. A mass of data has been compiled (there are more than 9,000 references) and carefully cross indexed so that the clinician or physiologist may obtain, with a minimum of effort, the ultimate in electrocardiographic knowledge, classified and interpreted according to the latest scientific standards. An attempt has been made to reconcile and combine contrasting schools of thought into a single system of electrocardiography. It is not intended to compete with existing textbooks of electrocardiography, but rather to supplement them. In the reviewer's opinion the book will prove to be of value mainly to those interested in basic electrocardiography, and as a source of reference. Throughout much of the text, references under any particular subject are simply quoted seriatim with no attempt to critically analyze the material. This is a necessary defect in a book of this type, but one which should not detract from its great value as a compendium of all material published from 1933 to 1951.

T. D.

CAUSES AND PREVENTION OF TUBERCULOSIS. By BRICE R. CLARKE, M.D., Formerly Medical Superintendent, Forster Green Hospital, Belfast, and Whiteabbey Hospital, Belfast. Pp. 288; 13 ills. Baltimore: The Williams and Wilkins Company, 1952. Price, $6.50.

THE author's thesis is that major emphasis in the effort to control tuberculosis should be placed on the prevention of infection and disease rather than on the treatment of persons with advanced disease who never should have been allowed to fall ill. By prevention the author means all methods which serve to identify the source of the disease and all measures that reduce the risk of exposure or progression in the infected. This takes into account the pathogenesis of tuberculosis in the primary and later stages and the influence of various factors such as race, heredity, age, sex, nutrition, occupation, physical environment and social condition.

The thesis is developed in the course of a masterful review of current knowledge of the epidemiology of tuberculosis in selected countries of Western Europe, the British Isles and the United States. On the basis of this review, the last five chapters discuss the uses of current knowledge for a planned program of prevention.

The prose is lucid and highly readable in a book packed with up-to-date information and a thoughtful, thought-provoking point of view.

D. O.

DIE VERSTANDENE FRAU. By DR. MED. EBERHARD SCHAETZING. Pp. 195. Munich: J. F. Lehmanns Verlag, 1952. Price, DM 11.50.

THE author has introduced into medical literature a new term "gynogogie." This refers to a dialectical relationship between physician (gynecologist) and patient whereby the latter, affected with neurotic gynecologic ailments, is led by the physician into revealing the true cause of what she is anxious about, or what she believes she has done wrongly or wherein she has sinned, or what does she really wish to achieve (what is the secondary gain). The questioning of the patient has been well systematized by the author and the signals by which she reveals what she really wishes to conceal are considered. The causes that give rise to functional amenorrhea, dysmenorrhea, and the like are set forth, and the causes of feminine impotence in its phases of anesthesia, frigidity, and dyspareunia are entered into. The various functional causes of leukorrhea are discussed, as well as the supposed effects of onanism and of coitus interruptus.

Freud, Jung, Adler, and Schultz-Hencke (who has coined the term "neopsychoanalysis") are given due recognition for their contributions to psychopathology.

On the whole the book is intended for gynecologists rather than for psychiatrists. The author treats his neurotic patients by suggestion and sometimes by hypnosis. He

deplores the fact that many of them have received excessive medical treatment (including the use of vitamins and endocrine preparations) at the hands of other physicians. Of course, the plan of treatment varies somewhat according to the individual case.

Considered as a whole the book is a distinct contribution to psychotherapy, and it would be well if the neurotic manifestations of the various systems of the body would be similarly systematized for the use of the various specialists. Philosophical reflections are rather amply dispersed throughout its pages. The diagrams represent overlapping ovals, one representing gynecology and the other psychiatry. "Life" says the author, "is eccentric," meaning that progress takes an oval or elliptical course rather than a circular one, and has this to quote for his method of dialectics, "In the beginning was the word."

M. M.

CORRELATIVE CARDIOLOGY. By CARL F. SHAFFER, M.D., F.A.C.P. Associate Professor of Clinical Medicine, Baylor University College of Medicine and DON W. CHAPMAN, M.D., F.A.C.P. Associate Professor of Medicine, Baylor University College of Medicine. Pp. 525, illustrated. Philadelphia: W. B. Saunders Company, 1952. Price, $9.50.

THE authors' purpose has been to "enable the student to comprehend the manifestation of the normal and abnormal cardiovascular system through simple, concise statements correlated with diagnostic illustrations." For the most part, the authors accomplish their purpose by outlining a wealth of facts. This book will probably be most useful for the student who is reviewing cardiology for an examination.

The deficiency in a book of this sort is the lack of description of the range of findings in a disease which forms the basis of good diagnostic medicine. Thus, most cases of aortic stenosis would be missed if the student made this diagnosis only in the presence of findings listed by the authors.

L. S.

THE HYPERSENSITIVE MIND. By GABRIEL LANGFELDT, M.D. Pp. 147. Copenhagen, Denmark: Ejnar Munksgaard, 1951. Price, not given.

THE author starts in with a worthy theme, namely, the sensitivity of the human mind. In his title, he promises to say something about prevention and treatment. In his recognition of the sensitive mind, he feels that this is partly hereditary and partly due to environmental influences. He does not seem at all sure as to where one leaves off and where the other begins. After mentioning the fact, however, that family experiences have a great deal to do with whether the mind becomes hypersensitive or not, he goes on to show how mind sensitivity and hypersensitivity shows itself in neurotics, psychopaths, and psychotics. Case histories are given. There is little organization to the observations which are made. Finally, the author disappoints us in his final chapter on Prevention and Treatment when he says "Quite generally it should be emphasized that individuals disposed to hypersensitive reactions should keep themselves in a physical healthy condition taking necessary respect to the usual mental hygiene rules, fresh air, exercise, sufficient sleep, and avoiding any type of intoxication especially that of alcohol and narcotic drugs." He also goes on to recommend Vitamin B_1 and electroshock therapy. In fact, he is quite enthusiastic about the latter.

The hypersensitive mind is an important subject, but the author's beginning demands that if he is consistent, he must proceed in his thesis to psychotherapeutic and sociological discussions as part of the therapeutic endeavor. Here is where the treatise falls down and gives us the therapeutic advice which is neither modern nor, according to the present consensus, effective.

O. E.

STEREOENCEPHALOTOMY (THALAMOTOMY AND RELATED PROCEDURES). Part I. METHODS AND STEREOTAXIS ATLAS OF THE HUMAN BRAIN. By E. A. SPIEGEL AND H. T. WYCIS. Temple University School of Medicine and Hospital, Philadelphia. Pp. 176; 79 ills. New York: Grune & Stratton, 1952. Price, About $6.50.

STEREOENCEPHALOTOMY is the attempt to produce sharply circumscribed lesions in subcortical ganglia and pathways by means of electrodes, the direction and position of which are exactly determined by mechanical guides. By modifying the Horsley-Clarke apparatus, the senior author (EAS), whose experimental work in Neurology is internationally known, has applied the method through his co-worker (HTW) to the human brain. This monograph describes the apparatus and its use. It provides a stereotoxic atlas of the human brain sections and gives tables of variability in measurements from the pineal gland or posterior commissure to various structures since the orientation point for the apparatus is based on one or the other locus.

The method, in the opinion of the reviewer, is still too intricate for general use. Nevertheless, it is the beginning of what may prove to be a valuable form of therapy in certain neurological diseases. R. G.

TUBERCLE BACILLUS AND LABORATORY METHODS IN TUBERCULOSIS. By M. A. SOLTYS, PH.D., D.M.VET., Lecturer in Bacteriology, University of Liverpool, C. A. ST. HILL, M.B., CH.B., and I. ANSELL, M.D., M.R.C.P. Pp. 202; 12 ills., and 6 tables. London: E. & S. Livingstone, Ltd., and Baltimore, Williams & Wilkins Co., 1952. Price, $4.50.

THE phthisiologist will find this a handy and fairly reliable reference volume. The biology of the tubercle bacillus is reviewed in succinct fashion with adequate references. Of considerable value to those concerned with laboratory methods in tuberculosis is the authors' selection and partial evaluation of technical procedures, including those used in testing susceptibility to chemotherapeutic agents. In the latter respect this booklet supplements the much more comprehensive and well-known volume by Arnold Rich.

E. S.

NEW BOOKS

The Practical Significance of Modern Cardiological Investigations. By T. E. LOWE, M.D., D.Sc., F.R.A.C.P., M.R.C.P., H. B. KAY, M.D., M.R.C.P., M.R.A.C.P., and H. A. LUKE, M.B., B.S., D.D.R. Pp. 206; 13 ills., 47 plates. Melbourne University Press, 1951 (American Representative: New York: Cambridge University Press American Branch, 1951). Price, $7.50.

THE subject of this monograph was that chosen for the Stawell Memorial Prize Essay of the British Medical Association (Victorian Branch) for the year 1949. It is essentially an assessment of the practical significance of modern cardiological investigations, but readers will not find sufficient details of any of the newer techniques to be of any real value to them, even in an introductory manner. T. D.

Proceedings of the Kessler Institute for Rehabilitation, Volume 1, Number 1, 1952. Pp. 49. West Orange, New Jersey: Kessler Institute for Rehabilitation, 1952.

THE Kessler Institute for Rehabilitation is well-recognized as outstanding in its work for the handicapped to make them self-supporting and productive members of the community. It is, therefore, noted with satisfaction that the Institute has begun to publish an annual medical bulletin reporting its experiences in this interesting and important field. The first number contains eight articles. They are very well done; the illustrations are excellent. R. K.

World Health Organization Technical Report Series No. 50. Expert Committee on the International Pharmacopoeia. Ninth Report including Third Report of the Subcommittee on Non-Proprietary Names. Pp. 36. Geneva: World Health Organization, 1952. Price, $.25.

Connective Tissue. Conference on Transactions of the 2nd Conference, May 24-25, 1951. Edited by CHARLES RAGAN. Pp. 190; 80 ills. New York: Josiah Macy, Jr. Foundation, 1952. Price, $3.50.

THIS is a report of the transactions of the second conference on Connective Tissues which took place in May, 1951. It presents in the form of a free discussion by 24 specially qualified investigators their latest views on the normal and disturbed physiology and structure of the connective tissue system. This book can be wholeheartedly recommended to those interested in this rapidly expanding and important field of inquiry. J. L.

Ophthalmic Glossary. By M. R. GOLDMAN, M.D., Assistant in Department of Ophthalmology, Montefiore and Passavant Hospitals, Pittsburgh, Pennsylvania. Pp. 40. Pittsburgh: Richard Rimbach, 1952. Price, $2.50.

THIS manual, designed not for ophthalmologists but for those who use ophthalmic terms, is a much needed publication. The glossary is incomplete and the definitions leave much to be desired. In an effort to keep the manual in the proper price level, the printing has been done in a mimeographic type. G. G.

Probleme der Schutzimpfung und die Bekämpfung der Rindertuberkulose. By PROF. DR. G. RAMON and G. FLÜCKIGER. Pp. 52. Stuttgart: Georg Thieme Verlag, 1952. Price, DM 7.20.

Research in Endocrinology. By AUGUST A. WERNER, M.D., St. Louis University School of Medicine. Pp. 285; illustrated. Belleville, Illinois: Belleville Daily Advocate, 1952. Price, not given.

The Origin of Life and the Evolution of Living Things. An Environmental Theory. By OLAN R. HYNDMAN, M.D. Pp. 648. New York: Hallmark-Hubner Press, 1952. Price, $8.75.

THE author's aim and style are indicated in the following direct quotation: "this is a plea to reopen the case for Lamarck in respect to his conviction that environment determines adaptive changes directly and in justification for which I humbly attempt to present a possible answer to the question". He has obviously spent much time and thought on this ambitious program; but the complexity of the subject combined with a deficiency in clarity of style and arrangement will make the book not worth while for most medical readers. E. K.

Early Care of the Seriously Wounded Man. By HENRY K. BEECHER, M.D., Chief, Department of Anesthesia, Massachusetts General Hospital, Boston. Pp. 32. Springfield, Illinois: Charles C Thomas, 1952. Price, $.75.

Cardiolipin Antigens. By M. C. PANGBORN, F. MALTANER, V. N. TOMPKINS, T. BEECHER, W. R. THOMPSON and M. R. FLYNN. Pp. 63; 1 ill. Geneva: World Health Organization, 1951. Price, $1.00.

Mind and Life. By SIR ARTHUR TANSLEY. Pp. 171. London, England: George Allen & Unwin, Ltd., Ruskin House. Agents for U. S., John DeGraff, Inc., New York, 1952. Price, $3.50.

THIS book contains a series of short essays on subjects such as the structure and energy of the mind, causation, determinism and free will, love and sex, psychological reality and spiritual values. The author subtitles his book, "An Essay in Simplification" and keeps to this promise by examining in a simple and yet profound manner some of our social problems and the tools by which we attempt to think them through and solve them. This book is recommended for those who wish to add a fresh viewpoint to the study of man and the nature and working of his mind. O. E.

Comparability of Statistics of Causes of Death According to the Fifth and Sixth Revisions of the International List. Bulletin of the World Health Organization Supplement 4. Pp. 59. Geneva: World Health Organization, 1952. (Columbia University Press, New York, Agents for United States.) Price, $.50.

NEW EDITIONS

The Treatment of Diabetes Mellitus. By ELLIOTT P. JOSLIN, A.M., M.D., Sc.D., HOWARD F. ROOT, M.D., PRISCILLA WHITE, M.D., Sc.D., and ALEXANDER MARBLE, A.M., M.D. 9th ed. Pp. 772; 26 ills., 1 in color. Philadelphia: Lea & Febiger, 1952. Price, $12.00.

THE ninth editon of this standard work, thoroughly revised and up-to-date, keeps it at the head of texts on diabetes. It should be on the desk of every practitioner and internist. R. K.

The Oculorotary Muscles. By RICHARD G. SCOBEE, B.A., M.D., F.A.C.S., Asst. Prof. of Ophthalmology, Washington University, St. Louis. 2nd ed. Pp. 512; 159 ills. St. Louis: C. V. Mosby Co., 1952. Price, $11.00.

IN the first edition, the author has written lucidly on the most complex and controversial subject in ophthalmology. The second edition is a definite improvement on the first. This book belongs in the library of all ophthalmologists. The style is very individualistic but it generously gives credit to others where the author has included much of the views of others. When the author departs from tradition he does so with either adequate argument or statistical evidence. While it is intended for the student, there is much of value for the seasoned practitioner. The book contains numerous points which many would choose to debate, but the essential teachings are basically sound. G. G.

Diseases of the Nervous System. By F. M. R. WALSHE, M.D., D.Sc., F.R.S., Fellow of the Royal College of Physicians of London, Fellow of University College, London. 7th ed. Pp. 365; 63 ills. Baltimore: Williams & Wilkins, 1952. Price, $5.50.

THIS book impressed the reviewer extremely favorably. It does what the author started to do, namely, write a textbook of neurology for "students and practitioners". In other words, it is not encyclopedic but contains the information necessary for those groups. It is very well presented, emphasizing the value of history, for instance. It even has a sufficient consideration of the psychoneuroses in it with a part of this on traumatic neurosis which I am sure will meet with the approval of all practicing neuropsychiatrists. Perhaps some of the discussions of therapy would not meet agreement on the part of everyone but that is no more than is true of all branches and many subjects of medicine. The author, of course, is a very well known, exceptionally capable neurologist and this book is recommended as the type of text for the purpose which such an individual would be expected to produce. S. G.

Physical Medicine in General Practice. Edited by WILLIAM BIERMAN, M.D. and SIDNEY LICHT, M.D., with Twenty-two Contributors. 3d ed. Pp. 798; 234 ills. New York: Paul B. Hoeber, Inc., 1952. Price, $12.50.

THIS is an excellent textbook which presents the important information on physical measures of treatment for the practitioner. The editors and contributors are well-recognized authorities with considerable clinical experience in their several fields. The basic procedures of heat (cold), massage and exercise are presented briefly and well including a short explanation of the physical principles, physiological action, indications, contraindications and techniques of application. In addition to chapters on hydrotherapy, diathermy, electrotherapy, infared and ultraviolet radiation, there are pertinent presentations of climate and spas, ultrasound, manipulation, muscle testing, occupational therapy, rehabilitation and the medico-legal responsibilities incident to the use of physical therapeutic measures. Finally, there are thirteen short chapters dealing with the clinical disorders in which physical medicine is most useful. A knowledge of the information contained in this book is valuable to every general practitioner and many specialists. O. F.